

► INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of stress and help you make the most of your study effort by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1)—especially what the new FRED computer-based testing (CBT) is likely to mean to you. As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it easy to become sidetracked and not achieve your goal of studying with maximum effectiveness. Common mistakes that students make when studying for the boards include the following:

- “Stressing out” owing to an inadequate understanding of the new computer-based format
- Not understanding how scoring is performed or what your score means
- Starting *First Aid* too late
- Starting to study too late
- Using inefficient or inappropriate study methods
- Buying the wrong books or buying more books than you can ever use
- Buying only one publisher’s review series for all subjects
- Not using practice examinations to maximum benefit
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using *First Aid* as your sole study resource

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies. To begin, it is important for you to understand what the examination involves.



The USMLE assesses a physician’s ability to apply knowledge, concepts, and principles that are important in health and disease and that constitute the basis of safe and effective patient care.²

► USMLE STEP 1—THE CBT BASICS

Some degree of concern about your performance on the USMLE Step 1 examination is both expected and appropriate. All too often, however, medical students become unnecessarily anxious about the examination. It is therefore important to understand precisely what the USMLE Step 1 involves. As you become familiar with Step 1, you can translate your anxiety into more efficient preparation.

The USMLE Step 1 is the first of three examinations that you must pass in order to become a licensed physician in the United States.¹ The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the

Federation of State Medical Boards (FSMB). In previous years, the examination was strictly organized around seven traditional disciplines: anatomy, behavioral science, biochemistry, microbiology, pathology, pharmacology, and physiology. In June 1991, the NBME began administering the “new” NBME Part I examination, which offered a more integrated and multidisciplinary format coupled with more clinically oriented questions.

In 1992, the USMLE replaced both the Federation Licensing Examination (FLEX) and the certifying examinations of the NBME.³ The USMLE now serves as the single examination system for U.S. medical students and international medical graduates (IMGs) seeking medical licensure in the United States.

How Is the CBT Structured?

The CBT Step 1 exam consists of seven question “blocks” of 50 questions each (see Figure 1) for a total of 350 questions, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions. Don’t be fooled! “Block 8” is the NBME survey.

These blocks were designed to reduce eyestrain and fatigue during the exam. Once an examinee finishes a particular block, he or she must click on a screen icon to continue to the next block. Examinees will **not** be able to go back and change answers to questions from any previously completed block. Changing answers, however, is allowed **within** a block of questions as long as time permits.

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses.

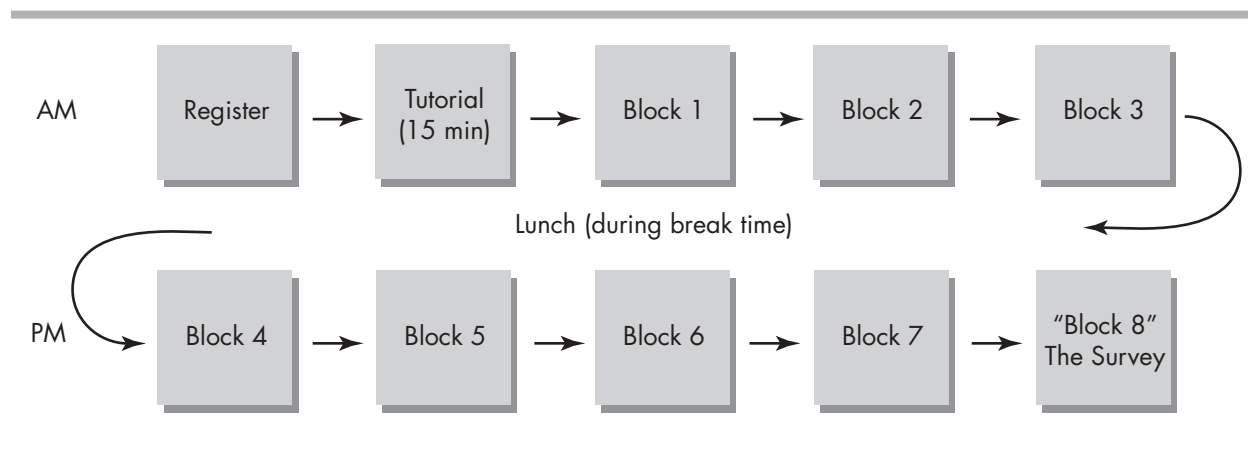


The CBT format of Step 1 is simply a computerized version of the former paper exam.



Don’t be fooled! After the last question block comes the NBME survey (“Block 8”).

FIGURE 1. Schematic of CBT Exam.





Skip the tutorial and add 15 minutes to your break time!

What Is the CBT Like?

Because of the unique environment of the CBT, it's important that you be familiar ahead of time with what your test-day conditions will be like. Familiarizing yourself with the testing interface before the exam can add 15 minutes to your break time! This is because a F tutorial, offered on exam day, may be skipped if you are already familiar with the exam procedures and the testing interface (see description of CD-ROM below). The 15 minutes is added to your allotted break time (should you choose to skip the tutorial).

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes digital watches, watches with computer communication and/or memory capability, cellular telephones, and electronic paging devices. Food and beverages are also prohibited. The testing centers are monitored by audio and video surveillance equipment.

In 2006, the USMLE will have completed its transition to FRED. FRED is a computer-based format that is similar to the old forms of CBT, with minor differences.



Test illustrations include:

- Gross photos
- Histology slides
- Radiographs
- EMs
- Line drawings

The typical question screen in FRED has a question followed by a number of choices on which an examinee can click, together with a number of navigational buttons on top. There is a countdown timer on the upper left-hand corner of the screen as well. There is also a button that allows the examinee to mark the question for review. If questions happen to be longer than the screen (which occurs very rarely), a scroll bar appears on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on the answer or leaves it blank, he or she must click the "Next" button to advance to the next question.

Some questions contain figures or color illustrations. These are typically situated to the right of the question. Although the contrast and brightness of the screen can be adjusted, there are no other ways to manipulate the picture (e.g., no zooming or panning).

The examinee can call up a window displaying normal lab values. In order to do so, he or she must hit the "Lab" icon on the top part of the screen. Afterward, the examinee will have the option to choose between "Blood," "Cerebrospinal," "Hematologic," or "Sweat and Urine." The normal-values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed laboratory values.

FRED allows the examinee to see a running list of the questions on the left part of the screen at all times. Also, with the new software, examinees will be able to highlight or cross out information using their mouse. Finally, there is an "Annotate" icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Examinees need to be careful with all of these new features, because failure to do so can cost valuable time!

What Does the CBT Format Mean to Me?

The significance of the CBT to you depends on the requirements of your school and your level of computer knowledge. If you hate computers and freak out whenever you see one, you might want to face your fears as soon as possible. Spend some time playing with a Windows-based system and pointing and clicking icons or buttons with a mouse. These are the absolute basics, and you won't want to waste valuable exam time figuring them out on test day. Your test taking will proceed by pointing and clicking, essentially without the use of the keyboard. The free CD is an excellent way to become familiar with the test interface.

For those who feel they would benefit, the USMLE offers an opportunity to take a simulated test, or "CBT Practice Session at a Prometric center." Students are eligible to take the three-and-one-half-hour practice session after they have received their fluorescent orange scheduling permit (see below).

The same USMLE Step 1 sample test items (150 questions) available on the CD or USMLE Web site, www.usmle.org, are used at these sessions. **No new items will be presented.** The session is divided into three one-hour blocks of 50 test items each and costs about \$42. The student receives a printed percent-correct score after completing the session. No explanations of questions are provided.

You may register for a practice session online at www.usmle.org.

How Do I Register to Take the Exam?

Step 1 or Step 2 applications may be printed from the USMLE Web site. The application allows applicants to select one of 12 overlapping three-month blocks in which to be tested (e.g., April–May–June, June–July–August). The application includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a fluorescent orange slip of paper called a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two unique numbers. One of these is known as your "scheduling number." You must have this number to make your exam appointment with Prometric. The other number is known as the "candidate identification number," or CIN. Examinees must enter their CINs at the Prometric workstation to access their exams. Prometric has no access to the codes. **Do not lose your permit!** You will not be allowed to take the boards unless you present this permit along with an unexpired, government-issued photo identification with your signature (such as a driver's license or passport). Make sure the name on your photo ID exactly matches the name appearing on your scheduling permit.

Once you receive your scheduling permit, you may call the Prometric toll-free number to arrange a time to take the exam. Although requests for taking



Keyboard shortcuts:

A–E—Letter choices.

Enter or spacebar—Move to next question.

Esc—Exit pop-up Lab and Exhibit windows.

Alt-T—Countdown timers for current session and overall test.



Ctrl-Alt-Delete are the keys of death during the exam. Don't touch them!



Test scheduling is on a "first-come, first-served" basis. It's important to call and schedule an exam date as soon as you receive your scheduling permit.



Testing centers are closed on major holidays and during the first two weeks of January.

the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a “first-come, first-served” basis, it is recommended that you telephone Prometric as soon as you have received your permit. After you’ve scheduled your exam, it’s a good idea to confirm your exam appointment with Prometric at least one week prior to your test date. Prometric does not provide written confirmation of exam date, time, or location. Be sure to read the *2006 USMLE Bulletin of Information* for further details.



Register six months in advance for seating and scheduling preference.

What If I Need to Reschedule the Exam?

You can change your date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or www.prometric.com. Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voice-mail message will not suffice. To avoid a rescheduling fee, you will need to request a change before noon EST at least five business days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

When Should I Register for the Exam?

Although there are no deadlines for registering for Step 1, you should plan to register at least six months ahead of your desired test date. This will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most U.S. medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, U.S. medical students should plan to register before January for a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation.

Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you must submit a new application along with another application fee.

Where Can I Take the Exam?

Your testing location is arranged with Prometric when you call for your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.

How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores three to six weeks after the examinee's test date. Scores are always released on a Wednesday. During peak times, score reports may take up to six weeks. Official information concerning the time required for score reporting is posted on the USMLE Web site.

What About Time?

Time is of special interest on the CBT exam. Here's a breakdown of the exam schedule:

15 minutes	Tutorial (skip if familiar)
7 hours	60-minute question blocks
45 minutes	Break time (includes time for lunch)

The computer will keep track of how much time has elapsed. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 72 seconds).

The computer will **not** warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need it and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from when you finish a block of questions to when you start the next block). After you finish one question block, you'll need to click the mouse when you are ready to proceed to the next block of questions.

Forty-five minutes is the minimum break time for the day. You can gain extra break time (but not time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time.

If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will enter onto your computer screen to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript.

The exam ends when all blocks have been completed or their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.



Be careful to watch the clock on your break time.



Gain extra break time by skipping the tutorial or finishing a block early.



Nearly three-fourths of Step 1 questions began with a description of a patient.

What Types of Questions Are Asked?

Although numerous changes had to be made for the CBT format, the question types are the same as in previous years.

One-best-answer items are the only multiple-choice format. Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the one best answer among the options. There are no “except,” “not,” or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam (see *Difficult Questions*, p. 23).

How Is the Test Scored?

Each Step 1 examinee receives a score report that has the examinee’s pass/fail status, two test scores, and a graphic depiction of the examinee’s performance by discipline and organ system or subject area (see Figures 2A and 2B). The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.



The mean Step 1 score for U.S. medical students rose from 200 in 1991 to 215 in 2000.

For 1999, the NBME provided two overall test scores based on the total number of items answered correctly on the examination (see Figure 3). The first score, the three-digit score, was reported as a scaled score in which the mean was 215 and the standard deviation was 20. The second score scale, the two-digit score, defines 75 as the minimum passing score (equivalent to a score of 179 on the first scale). A score of 82 is equivalent to a score of 200 on the first score scale. To avoid confusion, we refer to scores using the three-digit scale with a mean of 215 and a standard deviation of 20.

A score of 182 or higher is required to pass Step 1. Passing the CBT Step 1 is estimated to correspond to answering 60–70% of questions correctly. In 2004, the pass rates for first-time test takers from accredited U.S. and Canadian medical schools was 89% (see Table 1). These statistics prove it—you’re much more likely to pass than fail. Although the NBME may adjust the minimum passing score at any time, no further adjustment is expected for several years.

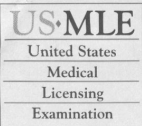


Passing the CBT Step 1 is estimated to correspond to answering 60–70% of the questions correctly.

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.

Consult the USMLE Web site or your medical school for the most current and accurate information regarding the examination.

FIGURE 2A . Sample Score Report—Front Page.

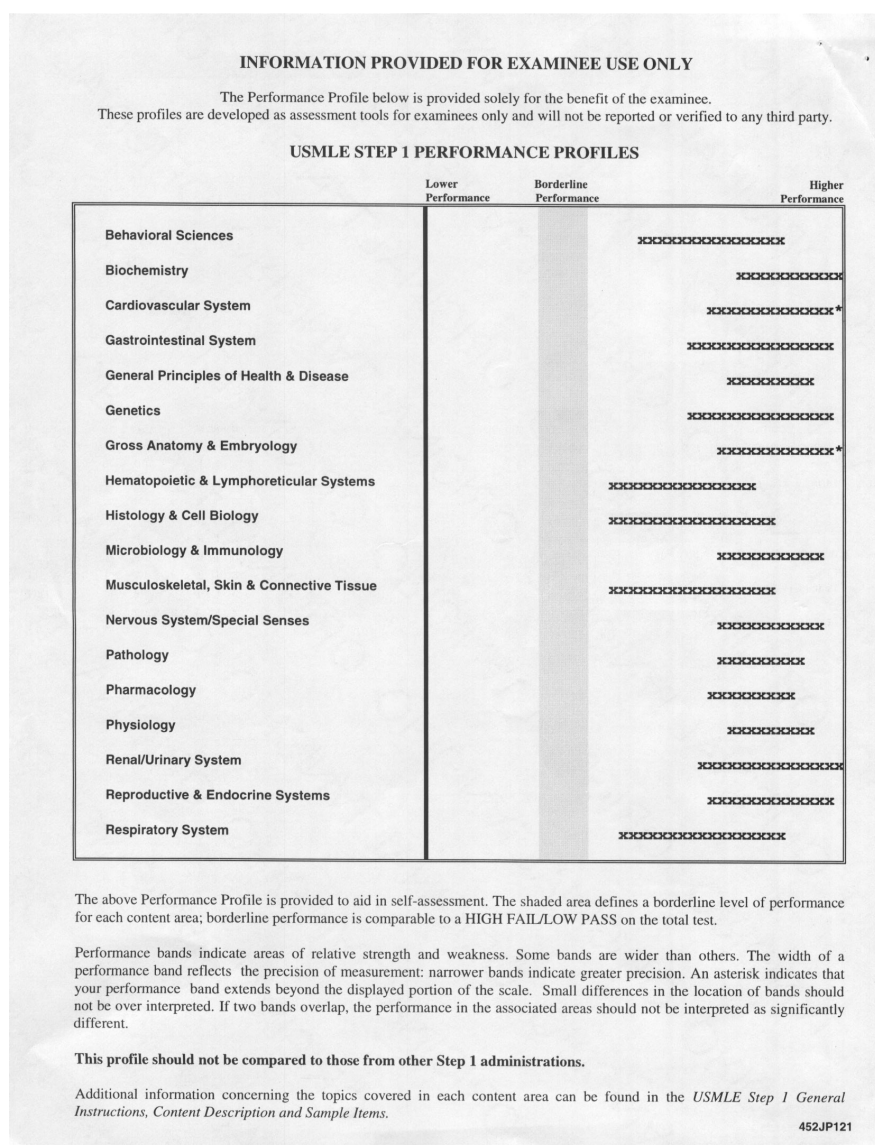
	UNITED STATES MEDICAL LICENSING EXAMINATION™ USMLE Step 1 is administered to students and graduates of U.S. and Canadian medical schools by the NATIONAL BOARD OF MEDICAL EXAMINERS® (NBME®) 3750 Market Street, Philadelphia, Pennsylvania 19104-3190. Telephone: (215) 590-9700		
STEP 1 SCORE REPORT			
<table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> Schmoe, Joe T Anytown, CA 12345 </td> <td style="width: 50%; vertical-align: top;"> USMLE ID: 1-234-567-8 Test Date: June 2002 </td> </tr> </table>		Schmoe, Joe T Anytown, CA 12345	USMLE ID: 1-234-567-8 Test Date: June 2002
Schmoe, Joe T Anytown, CA 12345	USMLE ID: 1-234-567-8 Test Date: June 2002		
<p>The USMLE is a single examination program for all applicants for medical licensure in the United States; it replaces the Federation Licensing Examination (FLEX) and the certifying examinations of the National Board of Medical Examiners (NBME Parts I, II and III). The program consists of three Steps designed to assess an examinee's understanding of and ability to apply concepts and principles that are important in health and disease and that constitute the basis of safe and effective patient care. Step 1 is designed to assess whether an examinee understands and can apply key concepts of the basic biomedical sciences, with an emphasis on principles and mechanisms of health, disease and modes of therapy. The inclusion of Step 1 in the USMLE sequence is intended to ensure mastery of not only the basic medical sciences undergirding the safe and competent practice of medicine in the present, but also the scientific principles required for maintenance of competence through lifelong learning. Results of the examination are reported to medical licensing authorities in the United States and its territories for use in granting an initial license to practice medicine. The two numeric scores shown below are equivalent; each state or territory may use either score in making licensing decisions. These scores represent your results for the administration of Step 1 on the test date shown above.</p>			
PASS	This result is based on the minimum passing score set by USMLE for Step 1. Individual licensing authorities may accept the USMLE-recommended pass/fail result or may establish a different passing score for their own jurisdictions.		
215	This score is determined by your overall performance on Step 1. For recent administrations, the mean and standard deviation for first-time examinees from U.S. and Canadian medical schools are approximately 215 and 20, respectively, with most scores falling between 175 and 255. A score of 179 is set by USMLE to pass Step 1. The standard error of measurement (SEM) [‡] for this scale is four points.		
85	This score is also determined by your overall performance on the examination. A score of 82 on this scale is equivalent to a score of 200 on the scale described above. A score of 75 on this scale, which is equivalent to a score of 182 on the scale described above, is set by USMLE to pass Step 1. The SEM [‡] for this scale is one point.		
<p><small>‡Your score is influenced both by your general understanding of the basic biomedical sciences and the specific set of items selected for this Step 1 examination. The SEM provides an estimate of the range within which your scores might be expected to vary by chance if you were tested repeatedly using similar tests.</small></p> <p style="text-align: right;"><small>121JP452</small></p> <p style="text-align: center;"><small>NOTE: Original score report has copy-resistant watermark.</small></p>			

What Does My Score Mean?

For students, the most important point with the Step 1 score is passing versus failing. Passing essentially means, “Hey, you’re on your way to becoming a fully licensed doc.”

Beyond that, the main point of having a quantitative score is to give you a sense of how you’ve done aside from the fact that you’ve passed the exam. The two-digit or three-digit score gauges how you have done with respect to the content on the exam.

Since the content of the exam is what drives the score, the profile of the exam is what remains relatively constant over the years. That is to say that each exam pro-

FIGURE 2B. Sample Score Report—Back Page.

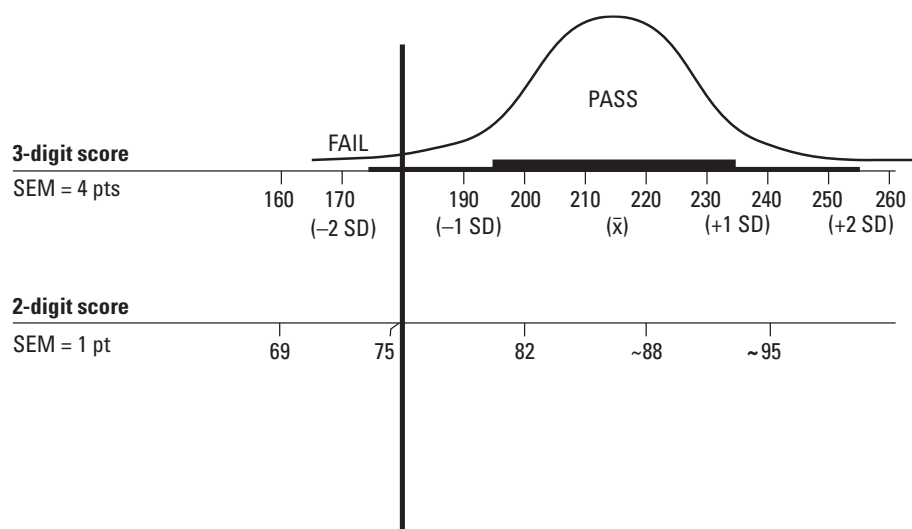
file includes a certain number of “very hard” questions along with “medium” and “easy” ones. The questions vary, but the profile of the exam doesn’t change much. This ensures that someone who scored 200 on the boards yesterday achieved a level of knowledge similar to that of the person who scored 200 four years ago.



Practice questions may be easier than the actual exam.

Official NBME/USMLE Resources

We strongly encourage students to use the free materials provided by the testing agencies (see p. 25) and to study in detail the following NBME publications, all of which are available on CD-ROM or at the USMLE Web site, www.usmle.org:

FIGURE 3. Scoring Scales for the USMLE Step 1.**TABLE 1. Passing Rates for the 2003–2004 USMLE Step 1.^a**

	2003		2004	
	No. TESTED	PASSING (%)	No. TESTED	PASSING (%)
NBME-registered examinees (U.S./Canadian)				
Allopathic students				
First-time takers	16,633	93	16,703	93
Repeaters	1,932	62	1,652	64
Allopathic total	18,565	90	18,355	91
Osteopathic students				
First-time takers	988	74	1,131	70
Repeaters	55	44	61	53
Osteopathic total	1,043	73	1,192	69
Total (U.S./Canadian)	19,608	89	19,547	89
FMG examinees (ECFMG ^b registrants)				
First-time takers	12,415	65	12,251	67
Repeaters	6,098	42	5,964	40
FMG total	18,513	57	18,215	58
Total Step 1 examinees	38,121	74	37,762	74

^aReflects the most current data available at the time of publishing.^bEducational Commission for Foreign Medical Graduates.

- *USMLE Step 1 2006 Computer-based Content and Sample Test Questions* (information given free to all examinees)
- *2006 USMLE Bulletin of Information* (information given free to all examinees)

The *USMLE Step 1 2006 Computer-based Content and Sample Test Questions* contains approximately 150 questions that are similar in format and content to the questions on the actual USMLE Step 1. This practice test offers one of the best methods for assessing your test-taking skills. However, it does not contain enough questions to simulate the full length of the examination, and its content represents a limited sampling of the basic science material that may be covered on Step 1. Most students felt that the questions on the actual 2005 exam were more challenging than those contained in these questions. Others report encountering a few near-duplicates of these questions on the actual Step 1. Presumably, these are “experimental” questions, but who knows! Bottom line: Know these questions!

The extremely detailed *Step 1 Content Outline* provided by the USMLE has not proved useful for students studying for the exam. The USMLE even states that “. . . the content outline is not intended as a guide for curriculum development or as a study guide.”⁴ We concur with this assessment.

The *2006 USMLE Bulletin of Information* is found on the CD-ROM. This publication contains detailed procedural and policy information regarding the CBT, including descriptions of all three Steps, scoring of the exams, reporting of scores to medical schools and residency programs, procedures for score rechecks and other inquiries, policies for irregular behavior, and test dates.

The NBME also offers the Comprehensive Basic Science Self-Assessment (CBSSA), which tests users on topics covered during basic science courses in a format similar to that of the USMLE Step 1 examination. The Web-based information provided via the CBSSA is intended for use as a study tool and not as an indicator of Step 1 performance. However, students who prepared for the examination using this Web-based tool found the format and content highly indicative of questions tested for the Step 1 examination.

The CBSSA exists in two forms: a standard-paced and a self-paced format, both of which consist of four sections of 50 questions each (a total of 400 multiple-choice items). The standard-paced format allows the user up to one hour to complete each section, reflecting the time limits of the actual exam. The self-paced format, however, places no time limit on answering the multiple-choice questions. Keep in mind that this bank of questions is available only on the Web. The NBME requires that users log on, register, and start within 30 days of registration. Once the assessment has begun, users are required to complete the sections within 20 days. Upon completion of the questions, the CBSSA will provide the user with a performance profile, indicating relative strengths and weaknesses, similar to the report profile for the USMLE Step 1 exam. However, please keep in mind that this self-assessment does not provide the user with a list of correct answers. Feedback from the self-assessment is entirely in the format of a performance profile and nothing more. The NBME charges \$45 for this ser-

vice, which is payable by credit card or money order. For more information regarding the CBSSA, please visit the NBME's Web site at www.nbme.org and click on the link for "NBME Web-based Self-Assessment Service."

► DEFINING YOUR GOAL

It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Your goal may depend on your school's requirements, your specialty choice, your grades to date, and your personal assessment of the test's importance. Do your best to define your goals early so that you can prepare accordingly.

Certain highly competitive residency programs, such as those in otolaryngology and orthopedic surgery, have acknowledged their use of Step 1 scores in the selection process. In such residency programs, greater emphasis may be placed on attaining a high score, so students who seek to enter these programs may wish to consider aiming for a very high score on the USMLE Step 1. However, a great number of residency programs value other criteria more highly than a high score on Step 1. For more information, fourth-year medical students who have recently completed the residency application process can be a valuable resource.



Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.



Some competitive residency programs use Step 1 scores in their selection process.

► TIMELINE FOR STUDY

Make a Schedule

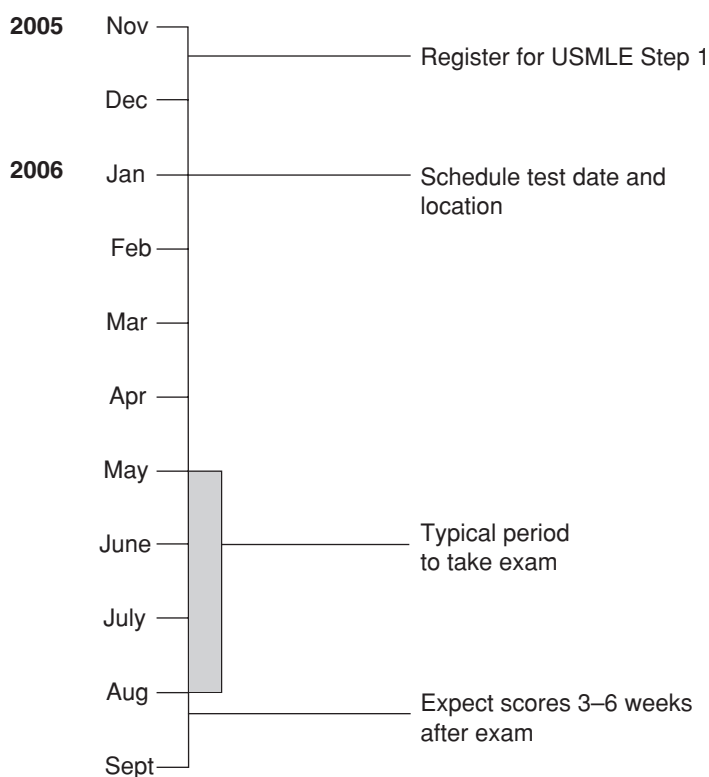
After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, and the difficulty of your ongoing coursework (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (e.g., SAT, MCAT).

Typically, students allot between five and seven weeks to prepare for Step 1. Some students reserve about a week at the end of their study period for final review; others save just a few days. When you have scheduled your date, do your best to keep to it. Recent studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date.⁵ This highlights the importance of working out a realistic schedule to which you can adhere.

Another important consideration is when you will study each subject. Some subjects lend themselves to cramming, whereas others demand a substantial long-term commitment. The "crammable" subjects for Step 1 are those for which concise yet relatively complete review books are available. (See Section IV for highly rated review and sample examination books.) Behavioral science



Time management is key. Customize your schedule to your goals and available time following any final exams.

FIGURE 4. Typical Timeline for the USMLE Step 1.

“Crammable” subjects should be covered later and less crammable subjects earlier.

and physiology are two subjects with concise review books. Three subjects with longer but quite complete review books are microbiology, pharmacology, and biochemistry. Thus, these subjects could be covered toward the end of your schedule, whereas other subjects (anatomy and pathology) require a longer time commitment and could be studied earlier. Many students prefer using a “systems-based” approach (e.g., GI, renal, cardiovascular) to integrate the material across basic science subjects. See Section III to study anatomy, pathology, physiology, and pharmacology facts by organ system.

Practically speaking, spending a given amount of time on a crammable or high-yield subject (particularly in the last few days before the test) generally produces more correct answers on the examination than spending the same amount of time on a low-yield subject. Student opinion indicates that knowing the crammable subjects extremely well probably results in a higher overall score than knowing all subjects moderately well.

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading *Gray’s Anatomy* in a couple of days is not a realistic goal! Revise your schedule regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. **Avoid students who stress you out.** Fo-

cus on a few top-rated books that suit your learning style—not on some obscure books your friends may pass down to you. Do not set yourself up for frustration. Accept the fact that you cannot learn it all. Maintain your sanity throughout the process.

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

Year(s) Prior

The USMLE asserts that the best preparation for the USMLE Step 1 resides in “broadly based learning that establishes a strong general foundation of understanding of concepts and principles in basic sciences.”⁶ We agree. Although you may be tempted to rely solely on cramming in the weeks and months before the test, you should not have to do so. The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as “shelf exams”) have been shown to be highly correlated with subsequent Step 1 scores.⁷ Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.⁸ The preponderance of your boards preparation should thus involve resurrecting dormant information that you have stored away during the basic science years.

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, the books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks.

Months Prior

Review test dates and the application procedure. In 2006, the testing for the USMLE Step 1 continues on a year-round basis (see Table 2). If you have any disabilities or “special circumstances,” contact the NBME as early as possible to discuss test accommodations (see p. 54, First Aid for the Student with a Disability).

Before you begin to study earnestly, simulate the USMLE Step 1 under “real” conditions to pinpoint strengths and weaknesses in your knowledge and test-taking skills. Be sure that you are well informed about the examination and that you have planned your strategy for studying. Consider what study methods you will use, the study materials you will need, and how you will obtain your materials. Plan ahead. Get advice from third- and fourth-year medical students who have recently taken the USMLE Step 1. There might be strengths and weaknesses in your school’s curriculum that you should take into account in decid-



Avoid burnout. Maintain proper diet, exercise, and sleep habits.



Buy review books early (first year) and use while studying for courses.



Simulate the USMLE Step 1 under “real” conditions before beginning your studies.

TABLE 2. 2006 USMLE Exams.

STEP	Focus	No. of Questions/ No. of Blocks	TEST SCHEDULE LENGTH OF CBT EXAM	PASSING SCORE
Step 1	Basic mechanisms and principles	350/7	One day (eight hours)	182
Step 2	Clinical diagnosis and disease pathogenesis	400/8	One day (nine hours)	174
Step 3	Clinical management	500/10	Two days (16 hours)	182

ing where to focus your efforts. You might also choose to share books, notes, and study hints with classmates. That is how this book began.



*In the final two weeks, focus
on review and endurance.
Avoid unfamiliar material.
Stay confident!*

Three Weeks Prior

Two to four weeks before the examination is a good time to resimulate the USMLE Step 1. You may want to do this earlier depending on the progress of your review, but do not do it later, when there will be little time to remedy defects in your knowledge or test-taking skills. Make use of remaining good-quality sample USMLE test questions, and try to simulate the computerized test conditions so that you get a fair assessment of your test performance. Recognize, too, that time pressure is increasing as more and more questions are framed as clinical vignettes. Most sample exam questions are shorter than the real thing. Focus on reviewing the high-yield facts, your own notes, picture books, and very short review books.



*Confirm your testing date at
least one week in advance.*

One Week Prior

Make sure you have your CIN (found on your scheduling permit) and other items necessary for the day of the examination, including a driver's license or other photo identification with your signature (make sure the name on your ID **exactly** matches that on your scheduling permit), an analog watch, and possibly earplugs. Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Visit the testing site (if possible) to get a better idea of the testing conditions. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site.

One Day Prior

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you do not have to deal with such details on the morning of the

exam. Do not study any new material. If you feel compelled to study, then quickly review short-term-memory material (e.g., Rapid Review) before going to sleep. However, do not quiz yourself, as you may risk becoming flustered and confused. Remember that regardless of how hard you studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night's sleep (e.g., massage, exercise, warm milk). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

Morning of the Exam

Wake up at your regular time and eat a normal breakfast. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as this may increase your anxiety. When you arrive at the test site, the proctor should give you a blue, laminated USMLE information sheet to read that will explain important things such as the use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

Remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. Avoid panic. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch and relax for a moment.

After the Test

Have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some “reentry” phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, book ratings, and the like (see p. xvii, How to Contribute). Sharing your experience benefits fellow medical students and IMGs.



No notes, books, calculators, pagers, recording devices, or digital watches are allowed in the testing area.



Arrive at the testing center 30 minutes before your scheduled exam time. If you arrive more than half an hour late, you will not be allowed to take the test.



Some students recommend reviewing certain “theme” topics that tend to recur throughout the exam.



If you pass Step 1, you are not allowed to retake the exam in an attempt to raise your score.

TABLE 3. Pass Rates for USMLE Step 1 Repeaters 1999.⁹

INITIAL SCORE	% PASS
176–178	83
173–175	74
170–172	71
165–169	64
160–164	54
150–159	31
< 150	0
Overall	67

► IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates. The CBT format allows an examinee who has failed the exam to retake it no earlier than the first day of the month after 60 days have elapsed since the last test date. Examinees will, however, be allowed to take the exam no more than three times within a 12-month period should they repeatedly fail.

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses (see Figure 2B). Study the performance profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test. If anxiety becomes a problem, however, seek appropriate counseling.

Fifty-two percent of the NBME-registered first-time takers who failed the June 1998 Step 1 repeated the exam in October 1998. The overall pass rate for that group in October was 60%. Eighty-five percent of those scoring near the old pass/fail mark of 176 (173–176) in June 1998 passed in October. However, 1999 pass rates varied widely depending on initial score (see Table 3, which reflects the most current data available at the time of publishing).

Although the NBME allows an unlimited number of attempts to pass Step 1, both the NBME and the FSMB recommend that licensing authorities allow a minimum of three and a maximum of six attempts for each Step examination.⁹ Again, review your school's policy regarding retakes.

► IF YOU FAILED

Even if you came out of the exam room feeling that you failed, seeing that failing grade can be traumatic, and it is natural to feel upset. Different people react in different ways: For some it is a stimulus to buckle down and study harder; for others it may “take the wind out of their sails” for a few days; and for still others it may lead to a reassessment of individual goals and abilities. In some instances, however, failure may trigger weeks or months of sadness, feelings of hopelessness, social withdrawal, and inability to concentrate—in other words, true clinical depression. If you think you are depressed, please seek help.

► STUDY METHODS

It is important to have a set of study methods for preparing for the USMLE Step 1. There is too much material to justify a studying plan that is built on random reading and memorization. Experiment with different ways of studying. You do not know how effective something might be until you try it. This is best done months before the test to determine what works and what you enjoy. Possible study options include the following:

- Studying review material in groups
- Creating personal mnemonics, diagrams, and tables
- Using *First Aid* as a framework on which to add notes
- Taking practice computer as well as pencil-and-paper tests (see Section IV for reviews)
- Attending faculty review sessions
- Making or sharing flash cards
- Reviewing old syllabi and notes
- Making cassette tapes of review material to study during commuting time
- Playing Trivial Pursuit–style games with facts and questions
- Getting away from home for an extended period to avoid distractions and to immerse yourself in studying

Study Groups

A good study group has many advantages. It can relieve stress, organize your time, and allow people with different strengths to exchange information. Study groups also allow you to pool resources and spend less money on review books and sample tests.

There are, however, potential problems associated with study groups. Above all, it is difficult to study with people who have different goals and study paces. Avoid study groups that tend to socialize more than study. If you choose not to belong to a study group, it may be a good idea to find a support group or a study partner with whom to keep pace and share study ideas. It is beneficial to get different perspectives from other students.

Mnemonics and Memorizing

Mnemonics are memory aids that work by linking isolated facts or abstract ideas to acronyms, pictures, patterns, rhymes, and stories—information that the mind tends to store well.¹¹ The best mnemonics are your own, and developing them takes work. The first step to creating a mnemonic is understanding the information to be memorized. Play around with the information and look for unique features that help you remember it. Effective mnemonics should link the topic with the facts in as specific and unambiguous a manner as possible. Keep the information fresh by quizzing yourself periodically with flash cards, in study groups, and so on. Do not make the common mistake of simply



Near the failure threshold, each three-digit scale point is equivalent to about 1.5 questions answered correctly.¹⁰



Balance individual and group study.



Developing good mnemonics takes time and work. Quiz yourself periodically. Do not simply reread highlighted material.

rereading highlighted review material. The material may start to look familiar, but that does not mean you will be able to remember it in another context during the exam. Strive to gain an understanding rather than rote memorization.

Review Sessions

Faculty review sessions can also be helpful. Review sessions that are geared specifically toward the USMLE Step 1 tend to be more helpful than general review sessions. By contrast, open “question and answer” sessions tend to be inefficient and not worth the time. Focus on reviews given by faculty who are knowledgeable in the content and testing format of the USMLE Step 1.

Commercial Courses

Commercial preparation courses can be helpful for some students, but they are expensive and require significant time commitment. The data also show that such courses have a limited impact on Step 1 scores.¹² However, this may reflect the fact that students who take such courses are concerned about their readiness to take the exam. Nevertheless, commercial courses are often an effective organizing tool for students who feel overwhelmed by the sheer volume of material involved in preparing for Step 1. Note, however, that multiple-week courses may be quite intense and may thus leave limited time for independent study.

► STUDY MATERIALS

Quality and Cost Considerations

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Many sample question books use poorly written questions or contain factual errors in their explanations.
- Explanations for sample questions vary in quality.



If a given review book is not working for you, stop using it no matter how highly rated it may be or how much it costs.

Basic Science Review Books

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the “perfect” book, as many subjects simply do not have one, and different students prefer different styles.

There are two types of review books: books that are stand-alone titles and books that are part of a series. The books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject. For example, charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.

You should also find out which books are up to date. Some new editions represent major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

Practice Tests

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students study almost solely from practice tests. Your best preview of the computerized exam can be found in the practice exams on the USMLE CD-ROM. Some students also recommend using computerized test simulation programs. In addition, students report that many current practice-exam books have questions that are, on average, shorter and less clinically oriented than the current USMLE Step 1.

After taking a practice test, try to identify concepts and areas of weakness, not just the facts that you missed. Do not panic if you miss a lot of questions on a practice examination; instead, use the experience you have gained to motivate your study and prioritize those areas in which you need the most work. Use quality practice examinations to improve your test-taking skills. Analyze your ability to pace yourself.

Clinical Review Books

Keep your eye out for more clinically oriented review books; purchase them early and begin to use them. A number of students are turning to Step 2 books, pathophysiology books, and case-based reviews to prepare for the clinical vignettes. Examples of such books include:

- *First Aid for the® Wards* (McGraw-Hill)
- *First Aid Clerkship* series (McGraw-Hill)
- *Blueprints* clinical series (Blackwell Science)
- *PreTest Physical Diagnosis* (McGraw-Hill)
- *Washington Manual* (Lippincott Williams & Wilkins)
- Various USMLE Step 2 review books



Most practice exams are shorter and less clinical than the real thing.



Use practice tests to identify concepts and areas of weakness, not just facts that you missed.

Texts, Syllabi, and Notes

Limit your use of texts and syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (e.g., drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized and to contain fewer diagrams and study questions than do top-rated review books.

► GENERAL STUDY STRATEGIES



Familiarize yourself with the commonly tested normal laboratory values.



Practice questions that include case histories or descriptive vignettes are critical for Step 1 preparation.



Practice and perfect test-taking skills and strategies well before the test date.

The USMLE Step 1 was created according to an integrated outline that organizes basic science material in a multidisciplinary approach. Broad-based knowledge is now more important than it was in the exams of prior years. The exam is designed to test basic science material and its application to clinical situations. A little over half of the questions include clinical vignettes, although some are brief. Some useful studying guidelines are as follows:

- Be familiar with the CBT tutorial. This will give you 15 minutes of extra break time.
- Use computerized practice tests in addition to paper exams.
- Consider doing a simulated test at a Prometric center.
- Practice taking 50 questions in one-hour bursts.
- Be familiar with the Windows environment.
- Consider scheduling a light rotation for your first clinical block in case you get a test date later than you expected.

Practice questions that include case histories or descriptive vignettes are critical in preparing for the clinical slant of the USMLE Step 1. The normal lab values provided on the computerized test are difficult to use and access. For quick reference, see the table of high-yield laboratory values on the inside back cover of this book.

► TEST-TAKING STRATEGIES

Your test performance will be influenced by both your fund of knowledge and your test-taking skills. You can increase your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

Pacing

You have seven hours to complete 350 questions. Note that each one-hour block contains 50 questions. This works out to about 72 seconds per question.

NBME officials note that time was not an issue for most takers of the CBT field test. However, pacing errors have in the past been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

Dealing with Each Question

There are several established techniques for efficiently approaching multiple-choice questions; see what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, work out all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices and the last sentence of the question and then read through the passage quickly, extracting only relevant information to answer the question. Try a variety of techniques on practice exams and see what works best for you.

Difficult Questions

Because of the exam's clinical emphasis, you may find that many of the questions appear workable but take more time than is available to you. It can be tempting to dwell on such questions for an excessive amount of time because you feel you are on the verge of "figuring it out," but resist this temptation and budget your time. Answer difficult questions with your best guess, mark them for review, and come back to them if you have time after you have completed the rest of the questions in the block. This will keep you from inadvertently leaving any questions blank in your efforts to "beat the clock."

Another reason for not dwelling too long on any one question is that certain questions may be **experimental** or may be **incorrectly phrased**. Moreover, not all questions are scored. Some questions serve as "embedded pretest items" that do not count toward your overall score.¹¹ In fact, anywhere from 10% to 20% of exam questions have been designated as experimental on past exams.

Guessing

There is **no penalty** for wrong answers. Thus, no test block should be left with unanswered questions. A hunch is probably better than a random guess. If you have to guess, we suggest selecting an answer you recognize over one that is totally unfamiliar to you.

Changing Your Answer

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other



Time management is an important skill for exam success.



Do not dwell excessively on questions that you are on the verge of "figuring out." Make your best guess and move on.



Remember that some questions may be experimental.



Your first hunch is not always correct.



Do not terminate the block too early. Carefully review your answers if possible.



Be prepared to read fast and think on your feet!



Step 1 vignettes usually describe diseases or disorders in their most classic presentation.

words, go with your “first hunch.” However, studies show that if you change your answer, you are twice as likely to change it from an incorrect answer to a correct one than vice versa. So if you have a strong “second hunch,” go for it!

Fourth-Quarter Effect (Avoiding Burnout)

Pacing and endurance are important. Practice helps develop both. Fewer and fewer examinees are leaving the examination session early. Use any extra time you might have at the end of each block to return to marked questions or to recheck your answers; you cannot add the extra time to any remaining blocks of questions or to your break time. Do not be too casual in your review or you may overlook serious mistakes. Remember your goals, and keep in mind the effort you have devoted to studying compared with the small additional effort you will need to maintain focus and concentration throughout the examination. Never give up. If you begin to feel frustrated, try taking a 30-second breather.

► CLINICAL VIGNETTE STRATEGIES

In recent years, the USMLE Step 1 has become increasingly clinically oriented. Students polled from 2003 exams report that nearly 80% of the questions were presented as clinical vignettes. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

What Is a Clinical Vignette?

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. Be prepared to read fast and think on your feet. Remember that the question is often indirectly asking something you already know.

Strategy

Remember that the Step 1 vignettes usually describe diseases or disorders in their most classic presentation. Look for buzzwords or cardinal signs (e.g., malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware, however, that the question may contain classic signs and symptoms instead of mere buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.

Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease.



Sometimes making a diagnosis is not necessary at all.

One strategy that many students suggest is to skim the questions and answer choices before reading a vignette, especially if the vignette is lengthy. This focuses your attention on the relevant information and reduces the time spent on that vignette. Sometimes you may not need much of the information in the vignette to answer the question.

► TESTING AGENCIES

National Board of Medical Examiners (NBME)

Department of Licensing Examination Services
3750 Market Street
Philadelphia, PA 19104-3102
(215) 590-9700
Fax: (215) 590-9457
E-mail: webmail@nbme.org
www.nbme.org

Educational Commission for Foreign Medical Graduates (ECFMG)

3624 Market Street, Fourth Floor
Philadelphia, PA 19104-2685
(215) 386-5900
Toll free within North America: (800) 500-8249
Fax: (215) 386-9196
E-mail: info@ecfmg.org
www.ecfmg.org

Federation of State Medical Boards (FSMB)

P.O. Box 619850
Dallas, TX 75261-9850
(817) 868-4000
Fax: (817) 868-4099
E-mail: usmle@fsmb.org
www.fsmb.org

USMLE Secretariat

3750 Market Street
Philadelphia, PA 19104-3190
(215) 590-9700
E-mail: webmail@nbme.org
www.usmle.org

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Special Situations

- ▶ First Aid for the International Medical Graduate
- ▶ First Aid for the Osteopathic Medical Student
- ▶ First Aid for the Podiatric Medical Student
- ▶ First Aid for the Student with a Disability

► FIRST AID FOR THE INTERNATIONAL MEDICAL GRADUATE

“International medical graduate” (IMG) is the term now used to describe any student or graduate of a non-U.S., non-Canadian, non-Puerto Rican medical school, regardless of whether he or she is a U.S. citizen. The old term “foreign medical graduate” (FMG) was replaced because it was misleading when applied to U.S. citizens attending medical schools outside the United States.

The IMG’s Steps to Licensure in the United States

If you are an IMG, you must go through the following steps (not necessarily in this order) to become licensed to practice in the United States. You must complete these steps even if you are already a practicing physician and have completed a residency program in your own country.

- Complete the basic sciences program of your medical school (equivalent to the first two years of U.S. medical school).
- Take the USMLE Step 1. You can do this while still in school or after graduating, but in either case your medical school must certify that you completed the basic sciences part of your school’s curriculum before taking the USMLE Step 1.
- Complete the clinical clerkship program of your medical school (equivalent to the third and fourth years of U.S. medical school).
- Take the USMLE Step 2 Clinical Knowledge (CK) exam. If you are still in medical school, you must have completed two years of school.
- Take the Step 2 Clinical Skills (CS) exam.
- Graduate with your medical degree.
- Then, send the ECFMG a copy of your degree and transcript, which they will verify with your medical school.
- Obtain an ECFMG certificate. To do this, candidates must accomplish the following:
 - Graduate from a medical school that is listed in the International Medical Education Directory (IMED). The list can be accessed at www.ecfm.org.
 - Pass Step 1, the Step 2 CK, and the Step 2 CS within a seven-year period.
 - Have their medical credentials verified by the ECFMG.
- The standard certificate is usually sent two weeks after all the above requirements have been fulfilled. You must have a valid certificate before entering an accredited residency program, although you may begin the application process before you receive your certification.
- Apply for residency positions in your field of interest, either directly or through the Electronic Residency Application Service (ERAS) and the National Residency Matching Program (“the Match”). To be entered into the Match, you need to have passed all the examinations necessary for ECFMG certification (i.e., Step 1, the Step 2 CK, and the Step 2 CS) by the rank order list deadline (February 22, 2006, for the 2006 Match). If you do not pass these exams by the deadline, you will be withdrawn from the Match.



More detailed information can be found in the 2006 edition of the ECFMG Information Booklet, available at www.ecfm.org/pubshome.html.



Applicants may apply online for the USMLE Step 2 CK or Step 2 CS or request an extension of the USMLE eligibility period at www.ecfm.org/usmle/index.html or www.ecfm.org/usmle/step2cs/index.html.

- Obtain a visa that will allow you to enter and work in the United States if you are not already a U.S. citizen or a green-card holder (permanent resident).
- If required for IMGs by the state in which your residency is located, obtain an educational/training/limited medical license. Your residency program may assist you with this application. Note that medical licensing is the prerogative of each individual state, not of the federal government, and that states vary with respect to their laws about licensing (although all 50 states recognize the USMLE).
- In order to begin your residency program, make sure your scores are valid.
- Once you have the ECFMG certification, take the USMLE Step 3 during your residency, and then obtain a full medical license. Once you have a license in any state, you are permitted to practice in federal institutions such as VA hospitals and Indian Health Service facilities in any state. This can open the door to “moonlighting” opportunities and possibilities for an H1B visa application. For details on individual state rules, write to the licensing board in the state in question or contact the FSMB.
- Complete your residency and then take the appropriate specialty board exams in order to become board certified (e.g., in internal medicine or surgery). If you already have a specialty certification in your home country (e.g., in surgery or cardiology), some specialty boards may grant you six months’ or one year’s credit toward your total residency time.
- Currently, many residency programs are accepting applications through ERAS. For more information, see *First Aid for the Match* or contact:

ECFMG/ERAS Program

P.O. Box 11746

Philadelphia, PA 19101-0746

(215) 386-5900

Fax: (215) 222-5641

e-mail: eras-support@ecfm.org

www.ecfm.org/eras

The USMLE and the IMG

The USMLE is a series of standardized exams that give IMGs a level playing field. It is the same exam series taken by U.S. graduates even though it is administered by the ECFMG rather than by the NBME. This means that passing marks for IMGs for Step 1, the Step 2 CK, and the Step 2 CS are determined by a statistical process that is based on the scores of U.S. medical students. For example, to pass Step 1, you will probably have to score higher than the bottom 8–10% of U.S. and Canadian graduates.

Timing of the USMLE

For an IMG, the timing of a complete application is critical. It is extremely important that you send in your application early if you are to garner the maximum number of interview calls. A rough guide would be to complete all exam requirements by August of the year in which you wish to apply. This

would translate into sending both your score sheets and your ECFMG certificate with your application.

In terms of USMLE exam order, arguments can be made for taking the Step 1 or the Step 2 CK exam first. For example, you may consider taking the Step 2 CK exam first if you have just graduated from medical school and the clinical topics are still fresh in your mind. However, keep in mind that there is a large overlap between Step 1 and Step 2 CK topics in areas such as pharmacology, pathophysiology, and biostatistics. You might therefore consider taking the Step 1 and Step 2 CK exams close together to take advantage of this overlap in your test preparation.

USMLE Step 1 and the IMG

What Is the USMLE Step 1? It is a computerized test of the basic medical sciences that consists of 350 multiple-choice questions divided into seven blocks.

Content. Step 1 includes test items in the following content areas:

- Anatomy
- Behavioral sciences
- Biochemistry
- Microbiology
- Pathology
- Pharmacology
- Physiology
- Interdisciplinary topics such as nutrition, genetics, and aging

Significance of the Test. Step 1 is required for the ECFMG certificate as well as for registration for the Step 2 CS. Since most U.S. graduates apply to residency with their Step 1 scores only, it may be the only objective tool available with which to compare IMGs with U.S. graduates.

Official Web Sites. www.usmle.org and www.ecfm.org/usmle.

Eligibility. Both students and graduates from medical schools that are listed in IMED are eligible to take the test. Students must have completed at least two years of medical school by the beginning of the eligibility period selected.

Eligibility Period. A three-month period of your choice.

Fee. The fee for Step 1 is \$685 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

Retaking the Exam. In the event that you failed the test, you can reapply and select an eligibility period that begins at least 60 days after the last attempt. You cannot take the same Step more than three times in any 12-month period. You cannot retake the exam if you passed. The minimum score to pass

the exam is 75 on a two-digit scale. To pass, you must answer roughly 60–65% of the questions correctly.

Statistics. In 2004, only 67% of ECFMG candidates passed Step 1 on their first attempt, compared with 93% of U.S. and Canadian medical students and graduates. Of note, 1994–1995 data showed that USFMGs (U.S. citizens attending non-U.S. medical schools) performed 0.4 SD lower than IMGs (non-U.S. citizens attending non-U.S. medical schools). Although their overall scores were lower, USFMGs performed better than IMGs on behavioral sciences. In general, students from non-U.S. medical schools perform worst in behavioral science and biochemistry (1.9 and 1.5 SDs below U.S. students) and comparatively better in gross anatomy and pathology (0.7 and 0.9 SD below U.S. students). Although derived from data collected in 1994–1995, these data may help you focus your studying efforts.

Tips. Although few if any students feel totally prepared to take Step 1, IMGs in particular require serious study and preparation to reach their full potential on this exam. It is also imperative that IMGs do their best on Step 1, as a poor score on Step 1 is a distinct disadvantage in applying for most residencies. Remember that if you pass Step 1, you cannot retake it in an attempt to improve your score. Your goal should thus be to beat the mean, because you can then confidently assert that you have done better than average for U.S. students. Good Step 1 scores will also lend credibility to your residency application and help you get into highly competitive specialties such as radiology, orthopedics, and dermatology.

Commercial Review Courses. Do commercial review courses help improve your scores? Reports vary, and such courses can be expensive. Many IMGs decide to try the USMLE on their own and then consider a review course only if they fail. Just keep in mind that many states require that you pass the USMLE within three attempts. (For more information on review courses, see Section IV.)

USMLE Step 2 CK and the IMG

What Is the Step 2 CK? It is a computerized test of the clinical sciences consisting of 370 multiple-choice questions divided into eight blocks. It can be taken at Prometric centers in the United States and several other countries.

Content. The Step 2 CK includes test items in the following content areas:

- Internal medicine
- Obstetrics and gynecology
- Pediatrics
- Preventive medicine
- Psychiatry
- Surgery
- Other areas relevant to the provision of care under supervision

Significance of the Test. The Step 2 CK is required for the ECFMG certificate. It reflects the level of clinical knowledge of the applicant. It tests clinical subjects, primarily internal medicine. Other areas that are tested are surgery, obstetrics and gynecology, pediatrics, orthopedics, psychiatry, ENT, ophthalmology, and medical ethics.

Official Web Sites. www.usmle.org and www.ecfm.org/usmle.

Eligibility. Students and graduates from medical schools that are listed in IMED are eligible to take the Step 2 CK. Students must have completed at least two years of medical school. This means that students must have completed the basic medical science component of the medical school curriculum by the beginning of the eligibility period selected.

Eligibility Period. A three-month period of your choice.

Fee. The fee for the Step 2 CK is \$685 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

Retaking the Exam. In the event that you fail the Step 2 CK, you can reapply and select an eligibility period that begins at least 60 days after the last attempt. You cannot take the same Step more than three times in any 12-month period. You cannot retake the exam if you passed.

Statistics. In 2003–2004, 75% of ECFMG candidates passed Step 2 on their first attempt, compared with 92% of U.S. and Canadian candidates.

Tips. It's better to take the Step 2 CK after you have completed your internal medicine rotation because most of the questions give clinical scenarios and ask you to make medical diagnoses and clinical decisions. In addition, because this is a clinical sciences exam, cultural and geographic considerations play a greater role than is the case with Step 1. For example, if your medical education gave you ample exposure to malaria, brucellosis, and malnutrition but little to alcohol withdrawal, child abuse, and cholesterol screening, you must work to familiarize yourself with topics that are more heavily emphasized in U.S. medicine. You must also have a basic understanding of the legal and social aspects of U.S. medicine, because you will be asked questions about communicating with and advising patients.

USMLE Step 2 CS and the IMG

What Is the Step 2 CS? The Step 2 CS is a test of clinical and communication skills administered as a one-day, eight-hour exam. It includes 10 to 12 encounters with standardized patients (15 minutes each, with 10 minutes to write a note after each encounter). Test results are valid indefinitely.

Content. The Step 2 CS tests the ability to communicate in English as well as interpersonal skills, data-gathering skills, the ability to perform a

physical exam, and the ability to formulate a brief note, a differential diagnosis, and a list of diagnostic tests. The areas that are covered in the exam are as follows:

- Internal medicine
- Surgery
- Obstetrics and gynecology
- Pediatrics
- Psychiatry
- Family medicine

Significance of the Test. The Step 2 CS is required for the ECFMG certificate. It has eliminated the Test of English as a Foreign Language (TOEFL) as a requirement for ECFMG certification.

Official Web Site. www.ecfmg.org/usmle/step2cs.

Eligibility. Students must have completed at least two years of medical school in order to take the test. That means students must have completed the basic medical science component of the medical school curriculum at the time they apply for the exam.

Fee. The fee for the Step 2 CS is \$1200.

Scheduling. You must schedule the Step 2 CS within **four months** of the date indicated on your notification of registration. You must take the exam within 12 months of the date indicated on your notification of registration.

Retaking the Exam. There is no limit to the number of attempts you can make to pass the Step 2 CS. However, you cannot retake the exam within 60 days of a failed attempt, and you cannot take it more than three times in a 12-month period.

Test Site Locations. The Step 2 CS is currently administered at the following five locations:

- Philadelphia, PA
- Atlanta, GA
- Los Angeles, CA
- Chicago, IL
- Houston, TX

For more information about the Step 2 CS exam, please refer to *First Aid for the Step 2 CS*.

USMLE Step 3 and the IMG

What Is the USMLE Step 3? It is a two-day computerized test in clinical medicine consisting of 480 multiple-choice questions and nine computer-based case simulations (CCS). The exam aims at testing your knowledge and

its application to patient care and clinical decision making (i.e., this exam tests if you can safely practice medicine independently and without supervision).

Significance of the Test. Taking Step 3 before residency is critical if an IMG is seeking an H1B visa and is a bonus that can be added to the residency application. Step 3 is also required to obtain a full medical license in the United States and can be taken during residency for this purpose.

Official Web Site. www.usmle.org.

Fee. The fee for Step 3 is \$590 (the total application fee can vary among states).

Eligibility. Most states require that applicants have completed one, two, or three years of postgraduate training (residency) before they apply for Step 3 and permanent state licensure. The exceptions are the 13 states mentioned below, which allow IMGs to take Step 3 at the beginning of or even before residency. So if you don't fulfill the prerequisites to taking Step 3 in your state of choice, simply use the name of one of the 13 states in your Step 3 application. You can take the exam in any state you choose regardless of the state that you mentioned on your application. Once you pass Step 3, it will be recognized by all states. Basic eligibility requirements for the USMLE Step 3 are as follows:

- Obtaining an MD or DO degree (or its equivalent) by the application deadline.
- Obtaining an ECFMG certificate if you are a graduate of a foreign medical school or are successfully completing a "fifth pathway" program (at a date no later than the application deadline).
- Meeting the requirements imposed by the individual state licensing authority to which you are applying to take Step 3. Please refer to www.fsmb.org for more information.

The following states do not have postgraduate training as an eligibility requirement to apply for Step 3:

- Arkansas
- California
- Connecticut
- Florida
- Louisiana
- Maryland
- Nebraska*
- New York
- South Dakota
- Texas
- Utah*
- Washington
- West Virginia

* Requires that IMGs obtain a "valid indefinite" ECFMG certificate.

The Step 3 exam is not available outside the United States. Applications can be found online at www.fsmb.org and must be submitted to the FSMB.

Residencies and the IMG

It is becoming increasingly difficult for IMGs to obtain residencies in the United States given the rising concern about an oversupply of physicians in the United States. Official bodies such as the Council on Graduate Medical Education (COGME) have recommended that the total number of residency slots be reduced. Furthermore, changes in immigration law are likely to make it much harder for noncitizens or legal residents of the United States to remain in the country after completing a residency.

In the residency Match, the number of U.S.-citizen IMG applications has been stable for the last few years, while the percentage accepted has slowly increased. For non-U.S.-citizen IMGs, applications fell from 7977 in 1999 to 5554 in 2005, while the percentage accepted significantly increased (see Table 4). This decrease in the total number of IMGs applying for the Match may be attributed to several factors:

- A decrease in the Step 2 CS passing rate to 80%.
- Increased difficulty obtaining U.S. visas.
- Increased expenses associated with the USMLE exams, ERAS, and travel to the United States.
- An increase in the number of IMGs who are withdrawing from the Match to sign a separate “pre-Match” contract with programs.

More information about residency programs can be obtained at www.ama-assn.org.

Visa Options for the IMG

If you are living outside the United States, you will need to apply for a visa that will allow you lawful entry into the United States in order to take the Step

TABLE 4. IMGs in the Match.

APPLICANTS	2003	2004	2005
U.S.-citizen IMGs	1987	2015	2091
% U.S. citizens accepted	55	55	55
Non-U.S.-citizen IMGs	5029	5671	5554
% non-U.S. citizens accepted	56	52	56
U.S. graduates (non-IMGs)	14,332	14,609	14,719
% U.S. graduates accepted	93	93	94

2 CS and/or do your interviews for residency. A B1 or B2 visitor visa may be issued by the U.S. consulate in your country. Citizens of some countries may have to undergo an additional security check that could take up to six months. Upon your entry into the United States, either the B1 or, more commonly, the B2 will be issued on your I-94. Both visas allow you a limited period within which to stay in the United States (two to six months) in order to take the exam. If the given period is not sufficient, you may apply for an extension before the expiration of your I-94.

Documents that are recommended to facilitate this process include the following:

- The Step 2 CS admission permit and a letter from the ECFMG (which explains why the applicant must enter the United States)
- Your medical diploma
- Transcripts from your medical school
- Your USMLE score sheets
- A sponsor letter or affidavit of support stating that you (if you are sponsoring yourself) or your sponsor will bear the expense of your trip and that you have sufficient funds to meet that expense
- An alien status affidavit

Individuals from certain countries may be allowed to enter the United States for up to 90 days without a visa under the Visa Waiver Program. See <http://uscis.gov>.

As an IMG, you need a visa to work or train in the United States unless you are a U.S. citizen or a permanent resident (i.e., hold a green card). Two types of visas enable you to accept a residency appointment in the United States: J1 and H1B. Most sponsoring residency programs (SRPs) prefer a J1 visa. Above all, this is because SRPs are authorized by the Department of Homeland Security (DHS) to issue a Form DS-2019 directly to an IMG. By contrast, SRPs must complete considerable paperwork, including an application to the Immigration and Labor Department, to apply to the DHS for an H1B visa on behalf of an IMG.

The J1 Visa

Also known as the Exchange Visitor Program, the J1 visa was introduced to give IMGs in diverse specialties the chance to use their training experience in the United States to improve conditions in their home countries. As mentioned above, the DHS authorizes most SRPs to issue Form DS-2019 in the same manner that I-20s are issued to regular international students in the United States.

To enable an SRP to issue a DS-2019, you must obtain a certificate from the ECFMG indicating that you are eligible to participate in a residency program in the United States. First, however, you must ask the Ministry of Health in your country to issue a statement indicating that your country needs physi-

cians with the skills you propose to acquire from a U.S. residency program. This statement, which must bear the seal of your country's government and must be signed by a duly designated government official, is intended to satisfy the U.S. Secretary of Health and Human Services (HHS) that there is such a need. The Health Ministry in your country should send this statement to the ECFMG (or they may allow you to mail it to the ECFMG).

How can you find out if the government of your country will issue such a statement? In many countries, the Ministry of Health maintains a list of medical specialties in which there is a need for further training abroad. You can also consult seniors in your medical school. A word of caution: If you are applying for a residency in internal medicine and internists are not in short supply in your country, it may help to indicate an intention to pursue a subspecialty after completing your residency training.

The text of your statement of need should read as follows:

Name of applicant for visa: _____. There currently exists in _____ (your country) a need for qualified medical practitioners in the specialty of _____. (Name of applicant for visa) has filed a written assurance with the government of this country that he/she will return to _____ (your country) upon completion of training in the United States and intends to enter the practice of medicine in the specialty for which training is being sought.

Stamp (or seal and signature) of issuing official of named country.
Dated _____

To facilitate the issuing of such a statement by the Ministry of Health in your country, you should submit a certified copy of the agreement or a contract from your SRP in the United States. The agreement or contract must be signed by you and the residency program official responsible for the training.

Armed with Form DS-2019, you should then go to the U.S. consulate closest to the residential address indicated in your passport. As for other nonimmigrant visas, you must show that you have a genuine nonimmigrant intent to return to your home country. You must also show that all your expenses will be paid.

When you enter the United States, bring your Form DS-2019 along with your visa. You are usually admitted to the United States for the length of the J1 program, designated as "D/S," or duration of status. The duration of your program is indicated on the DS-2019.

In the wake of the terrorist attacks of September 11, 2001, a number of new regulations have been introduced to improve the monitoring of exchange visitors during their time in the United States. All SRPs and students are currently required to register with the Student and Exchange Visitor Program (SEVP) via

the Student and Exchange Visitor Information System (SEVIS). SEVIS allows the DHS to maintain up-to-date information (e.g., enrollment status, current address) on exchange visitors. SEVIS Form DS-2019 is used for visa applications, admission, and change of status. Procedural details for this new legislation are still being hammered out, so contact your SRP or check <http://uscis.gov> for the most current information.

Duration of Participation. The duration of a resident's participation in a program of graduate medical education or training is limited to the time normally required to complete such a program. If you would like to get an idea of the typical training time for the various medical subspecialties, you may consult the *Directory of Medical Specialties*, published by Marquis Who's Who for the American Board of Medical Specialties. The authority charged with determining the duration of time required by an individual IMG is the State Department. The maximum amount of time for participation in a training program is ordinarily limited to seven years unless the IMG has demonstrated to the satisfaction of the ECFMG and the State Department that his or her home country has an exceptional need for the specialty in which he or she will receive further training. An extension of stay may be granted in the event that an IMG needs to repeat a year of clinical medical training or needs time for training or education to take an exam required for board certification.

Requirements After Entry into the United States. Each year, all IMGs participating in a residency program on a J1 visa must furnish the Attorney General of the United States with an affidavit (Form I-644) attesting that they are in good standing in the program of graduate medical education or training in which they are participating and that they will return to their home countries upon completion of the education or training for which they came to the United States.

Restrictions Under the J1 Visa. No later than two years after the date of entry into the United States, an IMG participating in a residency program on a J1 visa is allowed one opportunity to change his or her designated program of graduate medical education or training if his or her director approves that change.

The J1 visa includes a condition called the "two-year foreign residence requirement." The relevant section of the Immigration and Nationality Act states:

Any exchange visitor physician coming to the United States on or after January 10, 1977, for the purpose of receiving graduate medical education or training is automatically subject to the two-year home-country physical presence requirement of section 212(e) of the Immigration and Nationality Act, as amended. Such physicians are not eligible to be considered for section 212(e) waivers on the basis of "No Objection" statements issued by their governments.

The law thus requires that a J1 visa holder, upon completion of the training program, leave the United States and reside in his or her home country for a period of at least two years. Currently, the American Medical Association (AMA) is advocating that this period be extended to five years.

An IMG on a J1 visa is ordinarily not allowed to change from a J1 to most other types of visas or (in most cases) to change from J1 to permanent residence while in the United States until he or she has fulfilled the “foreign residence requirement.” The purpose of the foreign residence requirement is to ensure that an IMG uses the training he or she obtained in the United States for the benefit of his or her home country. The U.S. government may, however, waive the two-year foreign residence requirement under the following circumstances:

- If you as an IMG can prove that returning to your country would result in “exceptional hardship” to you or to members of your immediate family who are U.S. citizens or permanent residents;
- If you as an IMG can demonstrate a “well-founded fear of persecution” due to race, religion, or political opinions if forced to return to your country;
- If you obtain a “no objection” statement from your government; or
- If you are sponsored by an “interested governmental agency” or a designated state Department of Health in the United States.

Applying for a J1 Visa Waiver. IMGs who have sought a waiver on the basis of the last alternative have found it beneficial to approach the following potentially “interested government agencies”:

- **The Department of Health and Human Services.** Recently, HHS has expanded its role in reviewing J1 waiver applications. HHS’s considerations for a waiver have classically been as follows: (1) the program or activity in which the IMG is engaged is “of high priority and of national or international significance in an area of interest” to HHS; (2) the IMG must be an “integral” part of the program or activity “so that the loss of his/her services would necessitate discontinuance of the program or a major phase of it”; and (3) the IMG “must possess outstanding qualifications, training, and experience well beyond the usually expected accomplishments at the graduate, postgraduate, and residency levels and must clearly demonstrate the capability to make original and significant contributions to the program.” Under these criteria, HHS waivers are granted to physicians working in high-level biomedical research.

New rules will also allow HHS to review J1 waiver applications from community health centers, rural hospitals, and other health care providers. In the past, the U.S. Department of Agriculture (USDA) served as the interested federal government agency that reviewed waiver applications to allow foreign doctors to serve in rural underserved communities outside Appalachia, while the Appalachian Regional Commission (ARC) played that role for Appalachian communities. The USDA is no longer handling ap-

plications for J1 waivers. HHS will now review waiver applications for primary care practitioners and psychiatrists who have completed residency training within one year of application to practice in designated Health Professional Shortage Areas (HPSAs), Medically Underserved Areas and Populations (MUA/Ps), and Mental Health Professional Shortage Areas (MHPSAs). HHS waiver applications should be mailed to Joyce E. Jones, Executive Secretary, Exchange Visitor Waiver Review Board, Room 639-H, Hubert H. Humphrey Building, Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201; phone (202) 690-6174; fax (202) 690-7127.

- **The Department of Veterans Affairs.** With more than 170 health care facilities located in various parts of the United States, the VA is a major employer of physicians in this country. In addition, many VA hospitals are affiliated with university medical centers. The VA sponsors IMGs working in research, patient care (regardless of specialty), and teaching. The waiver applicant may engage in teaching and research in conjunction with clinical duties. The VA's latest guidelines (issued on June 22, 1994) provide that it will act as an interested government agency only when the loss of an IMG's services would necessitate the discontinuance of a program or a major phase of it and when recruitment efforts have failed to locate a U.S. physician to fill the position.

The procedure for obtaining a VA sponsorship for a J1 waiver is as follows: (1) the IMG should deal directly with the Human Resources Department at the local VA facility; and (2) the facility must request that the VA's chief medical director sponsor the IMG for a waiver. The waiver request should include the following documentation: (1) a letter from the director of the local facility describing the program, the IMG's immigration status, the health care needs of the facility, and the facility's recruitment efforts; (2) recruitment efforts, including copies of all job advertisements run within the preceding year; and (3) copies of the IMG's licenses, test results, board certifications, IAP-66 or SEVIS DS-2019 forms, and the like. The VA contact person in Washington, D.C., should be contacted by the local medical facility rather than by IMGs or their attorneys.

- **The Appalachian Regional Commission.** ARC sponsors physicians in certain places in the eastern and southern United States—namely, in Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Virginia, and West Virginia. Since 1992, ARC has sponsored approximately 200 primary care IMGs annually in counties within its jurisdiction that have been designated as HPSAs by HHS.

In accordance with its February 1994 revision of its J1 waiver policies, ARC requires that waiver requests initially be submitted to the ARC contact person in the state of intended employment. Contact information for each state can be found on the ARC Web site (www.arc.gov). If the state concurs, a letter from the state's governor recommending the waiver must

be addressed to Anne B. Pope, the new federal cochair of ARC. The waiver request should include the following: (1) a letter from the facility to Ms. Pope stating the proposed dates of employment, the IMG's medical specialty, the address of the practice location, an assertion that the IMG will practice primary care for at least 40 hours per week in the HPSA, and details as to why the facility needs the services of the IMG; (2) a J1 Visa Data Sheet; (3) the ARC federal cochair's J1 Visa Waiver Policy and the J1 Visa Waiver Policy Affidavit and Agreement with the notarized signature of the IMG; (4) a contract of at least three years' duration; (5) evidence of the IMG's qualifications, including a résumé, medical diplomas and licenses, and IAP-66 or SEVIS DS-2019 forms; and (6) evidence of unsuccessful attempts to recruit qualified U.S. physicians within the preceding six months. Copies of advertisements, copies of résumés received, and reasons for rejection must also be included. ARC will not sponsor IMGs who have been out of status for six months or longer.

Requests for ARC waivers are then processed in Washington, D.C. (ARC, 1666 Connecticut Avenue, N.W., Washington, D.C. 20009). ARC is usually able to forward a letter confirming that a waiver has been recommended to the requesting facility or attorney within 30 days of the request.

- **The Department of Agriculture.** At the time of publication, the USDA is no longer sponsoring J1 waivers. The scope of the HHS J1 waiver program has been expanded to fill the gap.
- **State Departments of Public Health.** There is no application form for a state-sponsored J1 waiver. However, regulations specify that an application must include the following documents: (1) a letter from the state Department of Public Health identifying the physician and specifying that it would be in the public interest to grant him or her a J1 waiver; (2) an employment contract that is valid for a minimum of three years and that states the name and address of the facility that will employ the physician and the geographic areas in which he or she will practice medicine; (3) evidence that these geographic areas are located within HPSAs; (4) a statement by the physician agreeing to the contractual requirements; (5) copies of all IAP-66 or SEVIS DS-2019 forms; and (6) a completed U.S. Information Agency (USIA) Data Sheet. Applications are numbered in the order in which they are received, since only 30 physicians per year may be granted waivers in a particular state under the Conrad State 30 program. Individual states may elect to participate or not to participate in this program. At the time of publication, nonparticipating states included Idaho, Oklahoma, and Wyoming, while Texas had suspended its J1 waiver program pending new legislation.

The H1B Visa

Since 1991, the law has allowed medical residency programs to sponsor foreign-born medical residents for H1B visas. There are no restrictions on changing the H1B visa to any other kind of visa, including permanent resident status (green card), through employer sponsorship or through close rela-

tives who are U.S. citizens or permanent residents. It is advisable for SRPs to apply for H1B visas as soon as possible in the official year (beginning October 1) when the new quota officially opens up.

According to the Web site www.immihelp.com, as of October 17, 2000, the following beneficiaries of approved H1B petitions are exempt from the H1B annual cap:

- Beneficiaries who are in J1 nonimmigrant status in order to receive graduate medical education or training, and who have obtained a waiver of the two-year home residency requirement;
- Beneficiaries who are employed at, or who have received an offer of employment at, an institution of higher education or a related or affiliated nonprofit entity;
- Beneficiaries who are employed by, or who have received an offer of employment from, a nonprofit research organization;
- Beneficiaries who are employed by, or who have received an offer of employment from, a governmental research organization;
- Beneficiaries who are currently maintaining, or who have held within the last six years, H1B status, and are ineligible for another full six-year stay as an H1B; and
- Beneficiaries who have been counted once toward the numerical limit and are the beneficiary of multiple petitions.

H1B visas are intended for “professionals” in a “specialty occupation.” This means that an IMG intending to pursue a residency program in the United States with an H1B visa needs to clear all three USMLE Steps before becoming eligible for the H1B. The ECFMG administers Steps 1 and 2, whereas Step 3 is conducted by the individual states. You will need to contact the FSMB or the medical board of the state where you intend to take Step 3 for details (see p. 33, USMLE Step 3 and the IMG).

H1B Application. An application for an H1B visa is filed not by the IMG but rather by his or her employment sponsor—in your case, by the SRP in the United States. If an SRP is willing to do so, you will be told about it at the time of your interview for the residency program.

Before filing an H1B application with the DHS, an SRP must file an application with the U.S. Department of Labor affirming that the SRP will pay at least the normal salary for your job that a U.S. professional would earn. After receiving approval from the Labor Department, your SRP should be ready to file the H1B application with the DHS. The SRP’s supporting letter is the most important part of the H1B application package; it must describe the job duties to make it clear that the physician is needed in a “specialty occupation” (resident) under the prevalent legal definition of that term.

Most SRPs prefer to issue a SEVIS Form DS-2019 for a J1 visa rather than file papers for an H1B visa because of the burden of paperwork and the attorney

costs involved in securing approval of an H1B visa application. Even so, a sizable number of SRPs are willing to go through the trouble, particularly if an IMG is an excellent candidate or if the SRP concerned finds it difficult to fill all the available residency slots (although this is becoming rarer with continuing cuts in residency slots). If an SRP is unwilling to file for an H1B visa because of attorney costs, you could suggest that you would be willing to bear the burden of such costs. The entire process of getting an H1B visa can take anywhere from 10 to 20 weeks.

H1B Premium Processing Service. According to the Web site www.myvisa.com, the DHS offers the opportunity to obtain processing of an H1B visa application within 15 calendar days. Within 15 days of receiving Form I-907, the DHS will mail you a notice of approval, request for evidence, intent to deny, or notice of investigation for fraud or misrepresentation. If the notice requires the submission of additional evidence or indicates an intent to deny, a new 15-day period will begin upon delivery to the DHS of a complete response to the request for evidence or notice of intent to deny. The fee for this service is \$1000. With this service, the total time needed to obtain an H1B visa has become significantly shorter than that required for the J1.

Although an H1B visa can be stamped by any U.S. consulate abroad, it is advisable that you have it stamped at the U.S. consulate where you first applied for a visitor visa to travel to the United States for interviews.

A Final Word

IMGs should also be aware of a new program called the National Security Entry-Exit Registration System, which aims to tighten up homeland security by keeping closer tabs on nonimmigrants residing in or entering the United States on temporary visas.

Male citizens or nationals of specific countries who are already residing in the United States may be required to report to a designated DHS office for registration, which includes being fingerprinted, photographed, and interviewed under oath. The official list of countries includes Bangladesh, Egypt, Indonesia, Jordan, Kuwait, Pakistan, Saudi Arabia, Afghanistan, Algeria, Bahrain, Eritrea, Lebanon, Morocco, North Korea, Oman, Qatar, Somalia, Tunisia, the United Arab Emirates, Yemen, Iran, Iraq, Libya, Sudan, and Syria. Different registration deadlines and criteria have been assigned to citizens of the above-mentioned countries, so please refer to <http://uscis.gov> for details.

If you are entering the United States, you may be registered at the port of entry if you are (1) a citizen or national of Iran, Iraq, Libya, Sudan, or Syria; (2) a nonimmigrant who has been designated by the State Department; or (3) any other nonimmigrant identified by immigration officers at airports, seaports, and land ports of entry in accordance with new regulation 8 CFR 264.1(f)(2). If you will be staying in the United States for more than 30 days, you will then

be required to register in person at a DHS district office within 30 days for an interview and will be required to reregister annually.

Once you are registered, certain special procedures will apply. If you leave the United States for any reason, you must appear in person before a DHS inspecting officer at a preapproved airport, seaport, or land port and leave the United States from that port on the same day. If you change your address, employment, or school, you must report to the DHS in writing within ten days using Form AR-11 SR. If any of these regulations are not followed, you may be considered out of status and subject to arrest, detention, fines, and/or removal from the United States, and any further application for immigration may be affected.

For the most up-to-date information regarding policies and procedures, please consult <http://uscis.gov>.

Summary

Despite some significant obstacles, a number of viable methods are available to IMGs who seek visas to pursue a residency program or eventually practice medicine in the United States. There is no doubt that the best alternative for an IMG is to obtain an H1B visa to pursue a medical residency. However, in cases where an IMG joins a residency program with a J1 visa, there are some possibilities for obtaining waivers of the two-year foreign residency requirement, particularly for those who are willing to make a commitment to perform primary care medicine in medically underserved areas.

Resources for the IMG

- **ECFMG**
3624 Market Street, Fourth Floor
Philadelphia, PA 19104-2685
(215) 386-5900
Fax: (215) 386-9196
www.ecfmg.org

The ECFMG telephone number is answered only between 9:00 A.M. and 12:30 P.M. and between 1:30 P.M. and 5:00 P.M. Monday through Friday EST. The ECFMG often takes a long time to answer the phone, which is frequently busy at peak times of the year, and then gives you a long voice-mail message—so it is better to write or fax early than to rely on a last-minute phone call. Do not contact the NBME, as all IMG exam matters are conducted by the ECFMG. The ECFMG also publishes an information booklet on ECFMG certification and the USMLE program, which gives details on the dates and locations of forthcoming USMLE and English tests for IMGs together with application forms. It is free of charge and is also available from the public affairs offices of U.S. embassies and consulates worldwide as well as from Overseas Educational Advisory Centers. You may order single copies of the handbook by calling (215) 386-5900,

preferably on weekends or between 6 P.M. and 6 A.M. Philadelphia time, or by faxing to (215) 387-9963. Requests for multiple copies must be made by fax or mail on organizational letterhead. The full text of the booklet is also available on the ECFMG's Web site at www.ecfmg.org.

- **FSMB**

P.O. Box 619850
Dallas, TX 75261-9850
(817) 868-4000
Fax: (817) 868-4099
www.fsmb.org

The FSMB has a number of publications available, including *The Exchange, Section I*, which gives detailed information on examination and licensing requirements in all U.S. jurisdictions. The cost is \$30. (Texas residents must add 8.25% state sales tax.) To obtain these publications, submit the online order form. Payment options include Visa or MasterCard. Alternatively, write to Federation Publications at the above address. All orders must be prepaid with a personal check drawn on a U.S. bank, a cashier's check, or a money order payable to the federation. Foreign orders must be accompanied by an international money order or the equivalent, payable in U.S. dollars through a U.S. bank or a U.S. affiliate of a foreign bank. For Step 3 inquiries, the telephone number is (817) 868-4041. You may e-mail the FSMB at usmle@fsmb.org or write to Examination Services at the address above.

- The Internet newsgroups misc.education.medical and bit.listserv.medforum can be valuable forums through which to exchange information on licensing exams, residency applications, and the like.
- Immigration information for IMGs is available from the sites of Siskind Susser, a firm of attorneys specializing in immigration law: www.visalaw.com/IMG/resources.html.
- Another source of immigration information can be found on the Web site of the law offices of Carl Shusterman, a Los Angeles attorney specializing in medical immigration law: www.shusterman.com.
- The AMA has dedicated a portion of its Web site to information on IMG demographics, residencies, immigration, and the like: www.ama-assn.org/ama/pub/category/17.html.
- International Medical Placement Ltd., a U.S. company specializing in recruiting foreign physicians to work in the United States, has a site at www.intlmedicalplacement.com.
- Two more useful Web sites are www.myvisa.com and www.immihelp.com.
- *First Aid for the International Medical Graduate*, 2nd ed., by Keshav Chander (2002; 313 pages; ISBN 0071385320), is an excellent resource written by a successful IMG. The book includes interviews with successful IMGs and students gearing up for the USMLE, complete "getting settled" information for new residents, and tips for dealing with possible social and cultural transition difficulties. The book provides useful advice on the U.S.

curriculum, the health care delivery system, and ethical issues—and the differences IMGs should expect. Dr. Chander points out the weaknesses often found in IMG hopefuls and suggests ways to improve their performance on standardized tests as well as on academic and clinical evaluations. As a bonus, the guide contains information on how to get good fellowships after residency. The bottom line is that this is a reassuring guide that can help IMGs boost their confidence and proficiency. A great “first of its kind” that will empower IMGs with information that they need to succeed.

Other books that may be useful and of interest to IMGs are as follows:

- *International Medical Graduates in U.S. Hospitals: A Guide for Directors and Applicants*, by Faroque A. Khan and Lawrence G. Smith (1995; ISBN 094312641x).
- *Insider's Guide for the International Medical Graduate to Obtain a Medical Residency in the U.S.A.*, by Ahmad Hakemi (1999; ISBN 1929803001).

► FIRST AID FOR THE OSTEOPATHIC MEDICAL STUDENT

What Is the COMLEX Level 1?

In 1995, the National Board of Osteopathic Medical Examiners (NBOME) introduced a new assessment tool called the Comprehensive Osteopathic Medical Licensing Examination, or COMLEX-USA. As with the former NBOME examination series, the COMLEX-USA is administered over three levels. In 1995, only Level 3 was administered, but by 1998 all three levels were implemented. The COMLEX-USA is now the only exam offered to osteopathic students. One goal of this changeover is to have all 50 states recognize this examination as equivalent to the USMLE. Currently, the COMLEX-USA exam sequence is accepted for licensure in all 50 states.

The COMLEX-USA series assesses osteopathic medical knowledge and clinical skills using clinical presentations and physician tasks. A description of the COMLEX-USA Written Examination Blueprints for each level, which outline the various clinical presentations and physician tasks that examinees will encounter, is given on the NBOME Web site. Another stated goal of the COMLEX-USA Level 1 is to create a more primary care-oriented exam that integrates osteopathic principles into clinical situations. As of July 1, 2004, the NBOME has initiated the administration of a Performance Evaluation/Clinical Skills component of the COMLEX-USA designated Level 2-PE, which candidates must pass in order to be eligible for the COMLEX Level 3.

To be eligible to take the COMLEX-USA Level 1, you must have satisfactorily completed at least one-half of your sophomore year in an American Osteopathic Association (AOA)-approved medical school. In addition, you must obtain verification that you are in good standing at your medical school via approval of your dean. Applications may be downloaded from the NBOME Web site.

For all three levels of the COMLEX-USA, raw scores are converted to a percentile score and a score ranging from 5 to 800. For Levels 1 and 2, a score of 400 is required to pass; for Level 3, a score of 350 is needed. COMLEX-USA scores are usually mailed eight weeks after the test date. The mean score on the June 2003 exam was 500 with a standard deviation of 79.

If you pass a COMLEX-USA examination, you are not allowed to retake it to improve your grade. If you fail, there is no specific limit to the number of times you can retake it in order to pass. Level 2 and 3 exams must be passed in sequential order within seven years of passing Level 1.

What Is the Structure of the COMLEX Level 1?

The final paper-and-pencil COMLEX Level 1 examination was administered on October 11–12, 2005. Starting in May 2006, the NBOME will begin delivering the COMLEX Level 1 by computer. This conversion to a computer-based examination will reduce test duration from two days to one day; de-

crease the total number of questions from about 800 to 400; and diminish the total testing time from 16 hours to 8 hours.

The computer-based COMLEX Level 1 examination will consist of multiple-choice questions that will remain in the same format as that of the paper-and-pencil COMLEX Level 1 examination. Most of the questions will be in one-best-answer format, but a small number will be matching-type questions. Some one-best-answer questions will be bundled together around a common question stem that will usually take the form of a clinical scenario. New question formats may gradually be introduced, but candidates will be notified if this occurs.

The content covered by the examination will remain similar. Because the computer-based test is new, it is difficult to predict what kinds of photos will be presented.

Questions will be grouped into sections of 50 questions, each in a manner similar to the USMLE. Reviewing and changing answers may be done only in the current section. A “review page” will be presented for each block in order to advise test takers of questions completed, questions marked for further review, and incomplete questions for which no answer has been given.

Only two optional breaks will be permitted during the test session. These breaks will be offered after the first two sections of the morning or afternoon session have been completed. This is an important departure from the USMLE. More information about the computer-based COMLEX-USA examinations can be obtained from www.nbome.org.

What Is the Difference Between the USMLE and the COMLEX-USA?

Although the COMLEX-USA and the USMLE are similar in scope, content, and emphasis, some differences are worth noting. For example, the COMLEX-USA Level 1 tests osteopathic principles in addition to basic science materials but does not emphasize lab techniques. In addition, although both exams often require that you apply and integrate knowledge over several areas of basic science to answer a given question, many students who took both tests in 2004 reported that the questions differed somewhat in style. Students reported, for example, that USMLE questions generally required that the test taker reason and draw from the information given (often a two-step process), whereas those on the COMLEX-USA exam tended to be more straightforward. Furthermore, USMLE questions were on average found to be considerably longer than those on the COMLEX-USA.

Students also commented that the COMLEX-USA utilized “buzzwords,” although limited in their use (e.g., “rose spots” in typhoid fever), whereas the USMLE avoided buzzwords in favor of descriptions of clinical findings or symptoms (e.g., rose-colored papules on the abdomen rather than rose spots). Finally, the 2004 USMLE had many more photographs than did the

COMLEX-USA. In general, the overall impression was that the USMLE was a more “thought-provoking” exam, while the COMLEX-USA was more of a “knowledge-based” exam.

Who Should Take Both the USMLE and the COMLEX-USA?

Aside from facing the COMLEX-USA Level 1, you must decide if you will also take the USMLE Step 1. We recommend that you consider taking both the USMLE and the COMLEX-USA under the following circumstances:

- **If you are applying to allopathic residencies.** Although there is growing acceptance of COMLEX-USA certification on the part of allopathic residencies, some allopathic programs prefer or even require passage of the USMLE Step 1. These include many academic programs, programs in competitive specialties (e.g., orthopedics, ophthalmology, or dermatology), and programs in competitive geographic areas (such as California). Fourth-year doctor of osteopathy (DO) students who have already matched may be a good source of information about which programs and specialties look for USMLE scores. It is also a good idea to contact program directors at the institutions you are interested in to ask about their policy regarding the COMLEX-USA versus the USMLE.
- **If you are unsure about your postgraduate training plans.** Successful passage of both the COMLEX-USA Level 1 and the USMLE Step 1 is certain to provide you with the greatest possible range of options when you are applying for internship and residency training.

The clinical coursework that some DO students receive during the summer of their third year (as opposed to their starting clerkships) is considered helpful in integrating basic science knowledge for the COMLEX-USA or the USMLE.

How Do I Prepare for the COMLEX-USA Level 1?

Student experience suggests that you should start studying for the COMLEX-USA four to six months before the test is given, as an early start will allow you to spend up to a month on each subject. The recommendations made in Section I regarding study and testing methods, strategies, and resources, as well as the books suggested in Section IV for the USMLE Step 1, hold true for the COMLEX-USA as well.

Another important source of information is in the *Examination Guidelines and Sample Exam*, a booklet that discusses the breakdown of each subject while also providing sample questions and corresponding answers. Many students, however, felt that this breakdown provided only a general guideline and was not representative of the level of difficulty of the actual COMLEX-USA. The sample questions did not provide examples of clinical vignettes, which made up approximately 25% of the exam. You will receive this publication with registration materials for the COMLEX-USA Level 1 exam, but you can also receive a copy and additional information by writing:

NBOME

8765 W. Higgins Road, Suite 200
 Chicago, IL 60631-4174
 (773) 714-0622
 Fax: (773) 714-0631

or by visiting the NBOME Web page at www.nbome.org.

Level 1 Practice Items is a new feature offered by the NBOME. It contains about 200 COMLEX-USA Level 1 items and answers. It is important to note that items in this booklet have been used in previous exams. The booklet costs \$15 and can be purchased via the NBOME Web site.

The 2004 COMLEX-USA exam consisted of 120 multiple-choice questions and 80 clinical vignette questions per test booklet. There were four test booklets, two of which had approximately ten matching questions. Each multiple-choice question accompanied a small case (about one to two sentences long).

In 2003, students reported an emphasis in certain areas. For example:

- There was an increased emphasis on lower limb anatomy.
- High-yield osteopathic manipulative technique (OMT) topics on the 2004 exam included basic craniosacral theory, sacral testing/diagnosis, lumbar mechanics, spinal motion and diagnosis, and an emphasis on the sympathetic and parasympathetic innervation of viscera.
- Specific topics were repeatedly tested on the exam. These included cardiovascular physiology and pathology, acid-base physiology, diabetes, benign prostatic hyperplasia, sexually transmitted diseases, measles, and rubella. Thyroid and adrenal function, neurology (head injury), specific drug treatments for bacterial infection, migraines/cluster headaches, and drug mechanisms also received heavy emphasis.
- Behavioral science questions were based on psychiatry.
- Since topics that were repeatedly tested appeared in all four booklets, students found it useful to review them in between the two test days. It is important to understand that the topics emphasized on the 2004 exam may not be stressed on the 2005 exam. However, some topics are heavily tested each year, so it may be beneficial to have a solid foundation of the above-mentioned topics.

► FIRST AID FOR THE PODIATRIC MEDICAL STUDENT

The National Board of Podiatric Medical Examiners (NBPME) tests are designed to assess whether a candidate possesses the knowledge required to practice as a minimally competent entry-level podiatrist. The NBPME examinations are used as part of the licensing process governing the practice of podiatric medicine. The NBPME exam is recognized by 44 states, the U.S. Army, the U.S. Navy, and the Canadian provinces of Alberta, British Columbia, and Ontario. Individual states use the examination scores differently; therefore, doctor of podiatric medicine (DPM) candidates should refer to the *NBPME Bulletin of Information: 2006 Examinations*.

The NBPME Part I is generally taken after the completion of the second year of podiatric medical education. Unlike the USMLE Step 1, there is no behavioral science section, nor is biomechanics tested on the NBPME Part I. The exam samples seven basic science disciplines: general anatomy (10%); lower extremity anatomy (22%); biochemistry (10%); physiology (12%); medical microbiology and immunology (15%); pathology (15%); and pharmacology (16%). A detailed outline of topics and subtopics covered on the exam can be found in the *NBPME Bulletin of Information*, available on the NBPME Web site.

Your NBPME Appointment

In early spring, your college registrar will have you fill out an application for the NBPME Part I. After your application and registration fees are received, you will be mailed the *NBPME Bulletin of Information: 2006 Examinations*. The exam will be offered at an independent location in each city with a podiatric medical school (New York, Philadelphia, Miami, Cleveland, Chicago, Des Moines, and Oakland/San Francisco). You may take the exam at any of these locations regardless of which school you attend. However, you must designate on your application which testing location you desire. Specific instructions about dates the exam is offered and registration deadlines can be found in the *NBPME Bulletin*.

Exam Format

The NBPME Part I is a written exam of 150 questions. The test consists entirely of multiple-choice questions, typically with four answer choices. Examinees have three hours in which to take the exam and are given scratch paper and a calculator, both of which must be turned in at the end of the exam. Some questions on the exam will be “trial questions.” These questions are evaluated as possible future board questions but are not counted in your score.

Interpreting Your Score

Three to four weeks following the exam date, test takers will receive their scores by mail. NBPME scores are reported as pass/fail, with a scaled score of

at least 75 needed to pass. Eighty-five percent of first-time test takers pass the NBPME Part I. Failing candidates receive a report with one score between 55 and 74 in addition to diagnostic messages intended to help identify strengths or weaknesses in specific content areas. If you fail the NBPME Part I, you must retake the entire examination at a later date. There is no limit to the number of times you can retake the exam.

Preparation for the NBPME Part I

Students suggest that you begin studying for the NBPME Part I at least three months prior to the test date. The suggestions made in Section I regarding study and testing methods for the USMLE Step 1 can be applied to the NBPME as well. This book should, however, be used as a supplement and not as the sole source of information. Keep in mind that you need only a passing score. Neither you nor your school or future residency will ever see your actual numerical score. Competing with colleagues should not be an issue, and study groups are beneficial to many.

Approximately 22% of the NBPME Part I focuses on lower extremity anatomy. In this area, students should rely on the notes and material that they received from their class. Remember, lower extremity anatomy is the podiatric physician's specialty—so everything about it is important. Do not forget to study osteology. Keep your old tests and look through old lower extremity class exams, since each of the podiatric colleges submits questions from its own exams. This strategy will give you an understanding of the types of questions that may be asked. On the NBPME Part I, you will see some of the same classic lower extremity anatomy questions you were tested on in school.

The NBPME, like the USMLE, requires that you apply and integrate knowledge over several areas of basic science in order to answer the questions. Students report that many questions emphasize clinical presentations; however, the facts in this book are very useful in helping students recall the various diseases and organisms. DPM candidates should expand on the high-yield pharmacology section and study antifungal drugs and treatments for *Pseudomonas*, methicillin-resistant *S. aureus*, candidiasis, and erythrasma. The high-yield section focusing on pathology is very useful; however, additional emphasis on diabetes mellitus and all its secondary manifestations, particularly peripheral neuropathy, should not be overlooked. Students should also focus on renal physiology and drug elimination, the biochemistry of gout, and neurophysiology, all of which have been noted to be important topics on the NBPME Part I exam.

A sample set of questions is found in the *NBPME Bulletin of Information: 2006 Examinations*. These samples are similar in difficulty to actual board questions. If you do not receive an *NBPME Bulletin* or if you have any questions regarding registration, fees, test centers, authorization forms, or score reports, please contact your college registrar or:

NBPME

P.O. Box 510

Bellefonte, PA 16823

(814) 357-0487

Fax: (814) 357-0581

E-mail: NBPMEOfc@aol.com

or visit the NBPME Web page at www.nbpme.info.

► FIRST AID FOR THE STUDENT WITH A DISABILITY

The USMLE provides accommodations for students with documented disabilities. The basis for such accommodations is the Americans with Disabilities Act (ADA) of 1990. The ADA defines a disability as “a significant limitation in one or more major life activities.” This includes both “observable/physical” disabilities (e.g., blindness, hearing loss, narcolepsy) and “hidden/mental disabilities” (e.g., attention-deficit hyperactivity disorder, chronic fatigue syndrome, learning disabilities).

To provide appropriate support, the administrators of the USMLE must be informed of both the nature and the severity of an examinee’s disability. Such documentation is required for an examinee to receive testing accommodations. Accommodations include extra time on tests, low-stimulation environments, extra or extended breaks, and zoom text.

Who Can Apply for Accommodations?

Students or graduates of a school in the United States or Canada that is accredited by the Liaison Committee on Medical Education (LCME) or the AOA may apply for test accommodations directly from the NBME. Requests are granted only if they meet the ADA definition of a disability. If you are a disabled student or a disabled graduate of a foreign medical school, you must contact the ECFMG (see below).

Who Is Not Eligible for Accommodations?

Individuals who do not meet the ADA definition of disabled are not eligible for test accommodations. Difficulties not eligible for test accommodations include test anxiety, slow reading without an identified underlying cognitive deficit, English as a second language, and learning difficulties that have not been diagnosed as a medically recognized disability.

Understanding the Need for Documentation

Although most learning-disabled medical students are all too familiar with the often exhausting process of providing documentation of their disability, you should realize that **applying for USMLE accommodation is different from these previous experiences**. This is because the NBME determines whether an individual is disabled solely on the basis of the guidelines set by the ADA. Previous accommodation does not in itself justify provision of an accommodation, so be sure to review the NBME guidelines carefully.

Getting the Information

The first step in applying for USMLE special accommodations is to contact the NBME and obtain a guidelines and questionnaire booklet. This can be obtained by calling or writing to:

Testing Coordinator

Office of Test Accommodations
National Board of Medical Examiners
3750 Market Street
Philadelphia, PA 19104-3102
(215) 590-9700

Internet access to this information is also available at www.nbme.org. This information is also relevant for IMGs, since the information is the same as that sent by the ECFMG.

Foreign graduates should contact the ECFMG to obtain information on special accommodations by calling or writing to:

ECFMG

3624 Market Street, Fourth Floor
Philadelphia, PA 19104-2685
(215) 386-5900

When you get this information, take some time to read it carefully. The guidelines are clear and explicit about what you need to do to obtain accommodations.

NOTES

This image shows a full page of blank, lined paper. It features approximately 30 evenly spaced horizontal grey lines across its entire width, providing a template for writing or drawing. The margins are consistent on all sides.

SECTION II

High-Yield General Principles

“There comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones.”

—Arthur Conan Doyle, *A Study in Scarlet*

“Never regard study as a duty, but as the enviable opportunity to learn.”

—Albert Einstein

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

—Gandhi

- ▶ Behavioral Science
- ▶ Biochemistry
- ▶ Embryology
- ▶ Microbiology and Immunology
- ▶ Pharmacology

The 2006 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that student authors and faculty have identified as high yield for board reviews. The information is presented in a partially organ-based format. Hence, Section II is devoted to the foundational principles of behavioral science, biochemistry, embryology, microbiology and immunology, and pharmacology. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, pathology, and pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are **not** ideal for learning complex or highly conceptual material for the first time. At the beginning of each subsection, we list supplementary high-yield clinical vignettes and topics that have appeared on recent exams in order to help focus your review.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the essential material, and as a result each entry is “incomplete.” Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update the database of high-yield facts annually to keep current with new trends in boards content as well as to expand our database of information. However, we must note that inevitably many other very high yield entries and topics are not yet included in our database.

We actively encourage medical students and faculty to submit entries and mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as diagrams, charts, and computer-based tutorials (see How to Contribute, p. xvii).

Disclaimer

The entries in this section reflect student opinions of what is high yield. Owing to the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. All errors and omissions will gladly be corrected if brought to the attention of the authors, either through the publisher or directly by e-mail.

HIGH-YIELD PRINCIPLES IN

Behavioral Science

“It’s psychosomatic. You need a lobotomy. I’ll get a saw.”

—Calvin, “Calvin & Hobbes”

A heterogeneous mix of epidemiology, biostatistics, ethics, psychology, sociology, and more falls under this heading. Many medical students do not study this discipline diligently because the material is felt to be “easy” or “common sense.” In our opinion, this is a missed opportunity. Each question gained in behavioral science is equal to a question in any other section in determining the overall score.

Many students feel that some behavioral science questions are less concrete and require an awareness of the social aspects of medicine. For example: If a patient does or says something, what should you do or say in response? These so-called quote questions now constitute much of the behavioral science section. We have included several examples in the high-yield clinical vignettes. Medical ethics and medical law are also appearing with increasing frequency. In addition, the key aspects of the doctor-patient relationship (e.g., communication skills, open-ended questions, facilitation, silence) are high yield. Basic biostatistics and epidemiology are very learnable and high yield. Be able to apply biostatistical concepts such as specificity and predictive values in a problem-solving format.

- ▶ High-Yield Clinical Vignettes
- ▶ Epidemiology
- ▶ Ethics
- ▶ Development
- ▶ Physiology
- ▶ Psychology

BEHAVIORAL SCIENCE—HIGH-YIELD CLINICAL VIGNETTES

■ Woman with anxiety about a gynecologic exam is told to relax and to imagine going through the steps of the exam.	What process does this exemplify?	Systematic desensitization.
■ 65-year-old man is diagnosed with incurable metastatic pancreatic adenocarcinoma. His family asks you, the doctor, not to tell the patient.	What do you do?	Assess whether telling patient will negatively affect his health. If not, tell him.
■ Man admitted for chest pain is medicated for ventricular tachycardia. The next day he jumps out of bed and does 50 pushups to show the nurses he has not had a heart attack.	What defense mechanism is he using?	Denial.
■ You find yourself attracted to your 26-year-old patient.	What do you say?	Nothing! The tone of the interview must be very professional; it is not acceptable to have any sort of romantic relationship with patients. If you feel your actions may be misinterpreted, invite a chaperone into the room.
■ Large group of people is followed over 10 years. Every 2 years, it is determined who develops heart disease and who does not.	What type of study is this?	Cohort study.
■ Girl can groom herself, can hop on 1 foot, and has an imaginary friend.	How old is she?	Four years old.
■ Man has flashbacks about his girlfriend's death 2 months ago following a hit-and-run accident. He often cries and wishes for the death of the culprit.	What is the diagnosis?	Normal bereavement.
■ 36-year-old woman with a strong family history of breast cancer refuses a mammogram because she heard it hurts.	What do you do?	Discuss the risks and benefits of not having a mammogram. Each patient must give her own informed consent to each procedure; if the patient refuses, you must abide by her wishes.

<ul style="list-style-type: none"> ■ 4-year-old girl complains of a burning feeling in her genitalia; otherwise she behaves and sleeps normally. Smear of discharge shows <i>N. gonorrhoeae</i>. 	<p>How was she infected?</p>	<p>Sexual abuse.</p>
<ul style="list-style-type: none"> ■ 72-year-old man insists on stopping treatment for his heart condition because it makes him feel “funny.” 	<p>What do you do?</p>	<p>Although you want to encourage the patient to take his medication, the patient has the final say in his own treatment regimen. You should investigate the “funny” feeling and determine if there are drugs available that don’t elicit this particular side effect.</p>

► BEHAVIORAL SCIENCE—EPIDEMIOLOGY/BIOSTATISTICS

Case-control study	Observational study. Sample chosen based on presence (cases) or absence (controls) of disease. Information collected about risk factors.	Often retrospective.
Cohort study	Observational study. Sample chosen based on presence or absence of risk factors. Subjects followed over time for development of disease.	The Framingham heart study was a large prospective cohort study.
Meta-analysis	Pooling data from several studies (often via a literature search) to achieve greater statistical power.	Cannot overcome limitations of individual studies or bias in study selection.
Clinical trial	Experimental study. Compares therapeutic benefits of 2 or more treatments, or treatment and placebo.	Highest-quality study when randomized and double-blind.
Bias	Occurs when 1 outcome is systematically favored over another. <ol style="list-style-type: none"> 1. Selection bias—nonrandom assignment to study group 2. Recall bias—knowledge of presence of disorder alters recall by subjects 3. Sampling bias—subjects are not representative; therefore results are not generalizable 4. Late-look bias—information gathered at an inappropriate time 	Ways to reduce bias: <ol style="list-style-type: none"> 1. Blind studies (single vs. double) 2. Placebo responses 3. Crossover studies (each subject acts as own control) 4. Randomization
Prevalence vs. incidence	$\text{Prevalence} = \frac{\text{total cases in population at a given time}}{\text{total population}}$ $\text{Incidence} = \frac{\text{new cases in population over a given time period}}{\text{total population at risk during that time}}$ <p>Prevalence \cong incidence \times disease duration. Prevalence > incidence for chronic diseases (e.g., diabetes). Prevalence = incidence for acute disease (e.g., common cold).</p>	<p>Incidence is new incidents.</p> <p>When calculating incidence, don't forget that people previously positive for a disease are no longer considered at risk.</p>
Sensitivity	<p>Number of true positives divided by number of all people with the disease.</p> <p>Probability of a positive test given that a person has the disease.</p> <p>False negative rate is equal to $1 - \text{sensitivity}$.</p> <p>High sensitivity is desirable for a screening test.</p>	SNOUT = SeNsitivity rules OUT.

Specificity	<p>Number of true negatives divided by number of all people without the disease.</p> <p>Probability of a negative test given that a person is free of the disease.</p> <p>False positive rate is equal to $1 - \text{specificity}$.</p> <p>High specificity is desirable for a confirmatory test.</p>	SPIN = SP ecificity rules IN .									
Predictive value											
Positive predictive value (PPV)	<p>Number of true positives divided by number of people who tested positive for the disease.</p> <p>The probability of having a condition given a positive test.</p>										
Negative predictive value (NPV)	<p>Number of true negatives divided by number of people who tested negative for the disease.</p> <p>The probability of not having the condition given a negative test.</p> <p>Unlike sensitivity and specificity, predictive values are dependent on the prevalence of the disease.</p> <p>The higher the prevalence of a disease, the higher the positive predictive value of the test. The lower the prevalence, the higher the negative predictive value.</p>										
		<div> <p>Disease</p> <table> <tr> <td></td><td>⊕</td><td>⊖</td></tr> <tr> <td>Test ⊕</td><td>a</td><td>b</td></tr> <tr> <td>⊖</td><td>c</td><td>d</td></tr> </table> <p>Sensitivity = $\frac{a}{a+c}$</p> <p>Specificity = $\frac{d}{b+d}$</p> <p>PPV = $\frac{a}{a+b}$</p> <p>NPV = $\frac{d}{c+d}$</p> </div>		⊕	⊖	Test ⊕	a	b	⊖	c	d
	⊕	⊖									
Test ⊕	a	b									
⊖	c	d									
Odds ratio vs. relative risk											
Odds ratio (OR)	<p>Odds of having disease in exposed group divided by odds of having disease in unexposed group.</p> <p>Odds are calculated within a group as number with disease divided by number without disease.</p> <p>Approximates relative risk if prevalence of disease is not too high.</p>	<div> <p>Disease</p> <table> <tr> <td></td><td>⊕</td><td>⊖</td></tr> <tr> <td>Test ⊕</td><td>a</td><td>b</td></tr> <tr> <td>⊖</td><td>c</td><td>d</td></tr> </table> </div>		⊕	⊖	Test ⊕	a	b	⊖	c	d
	⊕	⊖									
Test ⊕	a	b									
⊖	c	d									
Relative risk (RR)	<p>Used for case-control studies.</p> <p>Disease risk in exposed group divided by disease risk in unexposed group.</p> <p>Risk is calculated within a group as number with disease divided by total number of people in group.</p> <p>Used for cohort studies.</p>	<p>Odds ratio = $\frac{a/b}{c/d} = \frac{ad}{bc}$</p> <p>Relative risk = $\frac{a/(a+b)}{c/(c+d)}$</p> <p>Attributable risk = $\frac{a}{a+b} - \frac{c}{c+d}$</p>									

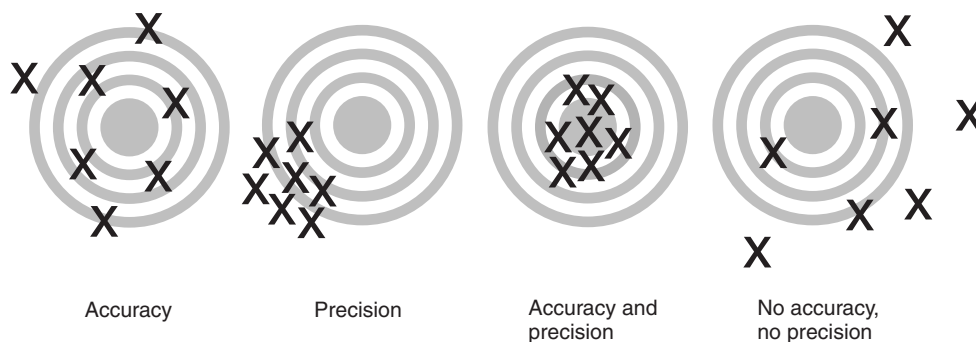
► BEHAVIORAL SCIENCE–EPIDEMIOLOGY/BIOSTATISTICS (*continued*)**Precision vs. accuracy**

Precision is:

1. The consistency and reproducibility of a test (reliability)
2. The absence of random variation in a test

Accuracy is the trueness of test measurements (validity).

Random error—reduced precision in a test.
Systematic error—reduced accuracy in a test.

**Statistical distribution**

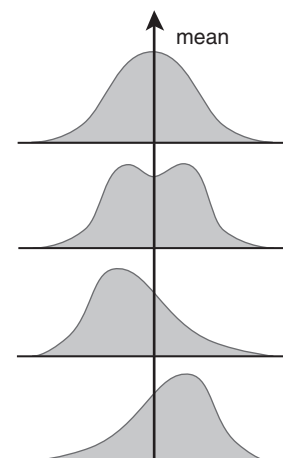
Terms that describe statistical distributions:

Normal \approx Gaussian \approx bell-shaped (mean = median = mode).

Bimodal is simply 2 humps.

Positive skew is asymmetry with tail on the right (mean > median > mode).

Negative skew has tail on the left (mean < median < mode).

**Statistical hypotheses**

Null (H_0)

Hypothesis of no difference (e.g., there is no association between the disease and the risk factor in the population).

Alternative (H_1)

Hypothesis that there is some difference (e.g., there is some association between the disease and the risk factor in the population).

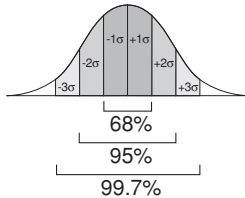
	Reality	
	H_1	H_0
Study results H_1	Power ($1 - \beta$)	α
H_0	β	

Type I error (α)

Stating that there is an effect or difference when none exists (to mistakenly accept the experimental hypothesis and reject the null hypothesis). p is judged against α , a preset level of significance (usually < .05).

p = probability of making a type I error.

If $p < .05$, then there is less than a 5% chance that the data will show something that is not really there. α = you “saw” a difference that did not exist—for example, convicting an innocent man.

Type II error (β)	Stating that there is not an effect or difference when one exists (to fail to reject the null hypothesis when in fact H_0 is false). β is the probability of making a type II error.	β = you did not “see” a difference that does exist—for example, setting a guilty man free.
Power ($1 - \beta$)	Probability of rejecting null hypothesis when it is in fact false. It depends on: <ol style="list-style-type: none"> 1. Total number of end points experienced by population 2. Difference in compliance between treatment groups (differences in the mean values between groups) 3. Size of expected effect 	If you \uparrow sample size, you \uparrow power. There is power in numbers. Power = $1 - \beta$.
Standard deviation vs. error	<p>n = sample size.</p> <p>σ = standard deviation.</p> <p>SEM = standard error of the mean.</p> <p>SEM = σ/\sqrt{n}.</p> <p>Therefore, SEM < σ and SEM decreases as n increases.</p>	<p>Normal (Gaussian) distribution:</p> 
Confidence interval	<p>Range of values in which a specified probability of the means of repeated samples would be expected to fall.</p> <p>CI = confidence interval.</p> <p>CI = range from [mean – Z(SEM)] to [mean + Z(SEM)].</p> <p>The 95% CI (corresponding to $p = .05$) is often used. For the 95% CI, $Z = 1.96$.</p>	If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and H_0 is not rejected. If the 95% CI for odds ratio or relative risk includes 1, H_0 is not rejected.
t-test vs. ANOVA vs. χ^2	<p>t-test checks difference between the means of 2 groups.</p> <p>ANOVA checks difference between the means of 3 or more groups.</p> <p>χ^2 checks difference between 2 or more percentages or proportions of categorical outcomes (not mean values).</p>	<p>Mr. T is mean.</p> <p>ANOVA = ANalysis Of VAriance of 3 or more variables.</p> <p>χ^2 = compare percentages (%) or proportions.</p>
Correlation coefficient (r)	<p>r is always between -1 and 1. Absolute value indicates strength of correlation between 2 variables.</p> <p>Coefficient of determination = r^2.</p>	
Disease prevention	<p>1°—prevent disease occurrence (e.g., vaccination).</p> <p>2°—early detection of disease (e.g., Pap smear).</p> <p>3°—reduce disability from disease (e.g., exogenous insulin for diabetes).</p>	<p>PDR:</p> <p>Prevent</p> <p>Detect</p> <p>Reduce disability</p>

► BEHAVIORAL SCIENCE–EPIDEMIOLOGY/BIOSTATISTICS (*continued*)**Important prevention measures**

Risk factor	Services
Diabetes	Eye, foot exams; urine tests
Drug use	Hepatitis immunizations; HIV, TB tests
Alcoholism	Influenza, pneumococcal immunizations; TB test
Overweight	Blood sugar tests for diabetes
Homeless, recent immigrant, inmate	TB test
High-risk sexual behavior	HIV, hepatitis B, syphilis, gonorrhea, chlamydia tests

Reportable diseases

Only some infectious diseases are reportable in all states, including AIDS, chickenpox, gonorrhea, hepatitis A and B, measles, mumps, rubella, salmonella, shigella, syphilis, and TB.
Other diseases (including HIV) vary by state.

B. A. SSSMMART

Chicken or you're **Gone**:

Hep **B**
Hep **A**
Salmonella
Shigella
Syphilis
Measles
Mumps
AIDS
Rubella
Tuberculosis
Chickenpox
Gonorrhea

Leading causes of death in the United States by age

Infants	Congenital anomalies, short gestation/low birth weight, sudden infant death syndrome, maternal complications of pregnancy, respiratory distress syndrome.
Age 1–14	Injuries, cancer, congenital anomalies, homicide, heart disease.
Age 15–24	Injuries, homicide, suicide, cancer, heart disease.
Age 25–64	Cancer, heart disease, injuries, suicide, stroke.
Age 65+	Heart disease, cancer, stroke, COPD, pneumonia, influenza.

Medicare and Medicaid

Medicare and Medicaid are federal programs that originated from amendments to the Social Security Act.
Medicare Part A = hospital; Part B = doctor bills.
Medicaid is federal and state assistance for very low income people.

Medicar**E** is for **E**lderly.
Medicai**D** is for **D**estitute.

Autonomy	Obligation to respect patients as individuals and to honor their preferences in medical care.	
Informed consent	<p>Legally requires:</p> <ol style="list-style-type: none"> 1. Discussion of pertinent information 2. Patient's agreement to the plan of care 3. Freedom from coercion 	Patients must understand the risks, benefits, and alternatives, which include no intervention.
Exceptions to informed consent	<ol style="list-style-type: none"> 1. Patient lacks decision-making capacity (not legally competent) 2. Implied consent in an emergency 3. Therapeutic privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity 4. Waiver—patient waives the right of informed consent 	
Decision-making capacity	<ol style="list-style-type: none"> 1. Patient makes and communicates a choice 2. Patient is informed 3. Decision remains stable over time 4. Decision is consistent with patient's values and goals 5. Decision is not a result of delusions or hallucinations 	The patient's family cannot require that a doctor withhold information from the patient.
Oral advance directive	Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive is specific, patient made a choice, and decision was repeated over time, the oral directive is more valid.	
Written advance directive	<p>Living will—patient directs physician to withhold or withdraw life-sustaining treatment if the patient develops a terminal disease or enters a persistent vegetative state.</p> <p>Durable power of attorney—patient designates a surrogate to make medical decisions in the event that the patient loses decision-making capacity. Patient may also specify decisions in clinical situations. Surrogate retains power unless revoked by patient. More flexible than a living will; supersedes living will if both exist.</p>	
Nonmaleficence	“Do no harm.” However, if benefits of an intervention outweigh the risks, a patient may make an informed decision to proceed.	
Beneficence	Physicians have a special ethical responsibility to act in the patient's best interest (“physician is a fiduciary”). Patient autonomy may conflict with beneficence. If the patient makes an informed decision, ultimately the patient has the right to decide.	
Confidentiality	Confidentiality respects patient privacy and autonomy. Disclosing information to family and friends should be guided by what the patient would want. The patient may also waive the right to confidentiality (e.g., insurance companies).	

► BEHAVIORAL SCIENCE—ETHICS (*continued*)**Exceptions to confidentiality**

1. Potential harm to others is serious
2. Likelihood of harm to self is great
3. No alternative means exist to warn or to protect those at risk
4. Physicians can take steps to prevent harm

Examples include:

1. Infectious diseases—physicians may have a duty to warn public officials and identifiable people at risk
2. The Tarasoff decision—law requiring physician to directly inform and protect potential victim from harm; may involve breach of confidentiality
3. Child and/or elder abuse
4. Impaired automobile drivers
5. Suicidal/homicidal patient—physician may hold patient involuntarily for a period of time

Malpractice

Civil suit under negligence requires:

1. Physician breach of duty to patient (**D**ereliction)
2. Patient suffers harm (**D**amage)
3. Breach of duty causes harm (**D**irect)

The most common factor leading to litigation is poor communication between physician and patient.

The 3 D's.

Unlike a criminal suit, in which the burden of proof is “beyond a reasonable doubt,” the burden of proof in a malpractice suit is “more likely than not.”

Ethical situations**Situation**

Patient is noncompliant.
 Patient has difficulty taking medications.
 Family members ask for information about patient's prognosis.
 A 17-year-old girl is pregnant and requests an abortion.

A terminally ill patient requests physician assistance in ending his life.
 Patient states that he finds you attractive.
 Patient refuses a necessary procedure or desires an unnecessary one.

Patient is angry about the amount of time he spent in the waiting room.

Patient is upset with the way he was treated by another doctor.

A child wishes to know more about his illness.

Patient continues to smoke, believing that cigarettes are good for him.

Appropriate response

Work to improve the physician-patient relationship.
 Provide written instructions; attempt to simplify treatment regimens.

Avoid discussing issues with relatives without the permission of the patient.

Many states require parental notification or consent for minors for an abortion. Parental consent is **not** required for emergency situations, treatment of STDs, medical care during pregnancy, prescriptions for contraceptives, and management of drug addiction.

In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physician may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient's life.

Ask direct, closed-ended questions and use a chaperone if necessary.

Romantic relationships with patients are **never** appropriate.

Attempt to understand why the patient wants/does not want the procedure. Address the underlying concerns. Avoid performing unnecessary procedures.

Apologize to the patient for any inconvenience. Stay away from efforts to explain the delay.

Suggest that the patient speak directly to that physician regarding his concerns. If the problem is with a member of the office staff, tell the patient you will speak to that individual.

Ask what the parents have told the child about his illness. Parents of a child decide what information can be relayed about the illness.

Ask how the patient feels about his smoking. Offer advice on cessation if the patient seems willing to make an effort to quit.

► BEHAVIORAL SCIENCE—DEVELOPMENT

Apgar score (at birth)	Score 0–2 at 1 and 5 minutes in each of 5 categories: 1. Color (blue/pale, trunk pink, all pink) 2. Heart rate (0, < 100, 100+) 3. Reflex irritability (0, grimace, grimace + cough) 4. Muscle tone (limp, some, active) 5. Respiratory effort (0, irregular, regular) 10 is perfect score.	APGAR: Appearance (color) Pulse Grimace Activity Respiration
Low birth weight	Defined as < 2500 g. Associated with greater incidence of physical and emotional problems. Caused by prematurity or intrauterine growth retardation. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.	
Infant deprivation effects	Long-term deprivation of affection results in: 1. ↓ muscle tone 2. Poor language skills 3. Poor socialization skills 4. Lack of basic trust 5. Anaclitic depression 6. Weight loss 7. Physical illness Severe deprivation can result in infant death.	The 4 W's: Weak, Wordless, Wanting (socially), Wary. Deprivation for > 6 months can lead to irreversible changes.
Anaclitic depression	Depression in an infant owing to continued separation from caregiver—can result in failure to thrive. Infant becomes withdrawn and unresponsive.	
Regression in children	Children regress to younger behavior under stress—physical illness, punishment, birth of a new sibling, tiredness. An example is bed-wetting in a previously toilet-trained child when hospitalized.	
Child abuse		
Evidence	Physical abuse Healed fractures on x-ray, cigarette burns, subdural hematomas, multiple bruises, retinal hemorrhage or detachment	Sexual abuse Genital/anal trauma, STDs, UTIs
Abuser	Usually female and the 1° caregiver	Known to victim, usually male
Epidemiology	~3000 deaths/year in the United States	Peak incidence 9–12 years of age

Developmental milestones

Approximate age	Motor milestone	Cognitive/social milestone
Infant		
3 mo	Holds head up, Moro reflex disappears	Social smile
4–5 mo	Rolls front to back, sits when propped	Recognizes people
7–9 mo	Sits alone, crawls	Stranger anxiety, orients to voice
12–14 mo	Upgoing Babinski disappears	
15 mo	Walks	Few words, separation anxiety
Toddler		
12–24 mo	Climbs stairs, stacks 3 blocks	Object permanence
18–24 mo	Stacks 6 blocks	Rapprochement
24–48 mo		Parallel play
24–36 mo		Core gender identity
Preschool		
30–36 mo	Stacks 9 blocks	Toilet training
3 yrs	Rides tricycle, copies line or circle drawing	Group play
4 yrs	Simple drawings (stick figure), hops on 1 foot	Cooperative play, imaginary friends
School age		
6–11 yrs	Reads; understands death	Development of conscience (superego), same-sex friends, identification with same-sex parent
Adolescence (puberty)		
11 yrs (girls)		Abstract reasoning (formal operations), formation of personality
13 yrs (boys)		

Changes in the elderly

<ol style="list-style-type: none"> Sexual changes—sexual interest does not ↓ Men: slower erection/ejaculation, longer refractory period Women: vaginal shortening, thinning, and dryness Sleep patterns—↓ REM sleep, ↓ slow-wave sleep, ↑ sleep latency, ↑ awakenings during the night Common medical conditions—arthritis, hypertension, heart disease, osteoporosis Psychiatric problems (e.g., depression) become more prevalent ↑ suicide rate 	<p>Additional changes with aging:</p> <ol style="list-style-type: none"> ↓ vision, hearing, immune response, bladder control ↓ renal, pulmonary, GI function ↓ muscle mass, ↑ fat <p>Intelligence does not ↓.</p>
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Grief

Normal bereavement characterized by shock, denial, guilt, and somatic symptoms. Typically lasts 6 months to 1 year. May experience illusions. Pathologic grief includes excessively intense or prolonged grief or grief that is delayed, inhibited, or denied. May experience depressive symptoms, delusions, and hallucinations.

► BEHAVIORAL SCIENCE—DEVELOPMENT (*continued*)

Kübler-Ross grief stages	Denial, Anger, Bargaining, Grieving, Acceptance. Stages do not necessarily occur in this order, and > 1 stage can be present at once.	Death Arrives Bringing Grave Adjustments.
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► BEHAVIORAL SCIENCE—PHYSIOLOGY

Stress effects	Stress induces production of free fatty acids, 17-OH corticosteroids, lipids, cholesterol, catecholamines; affects water absorption, muscular tonicity, gastrocolic reflex, and mucosal circulation. May exacerbate certain physical disorders (including CHF, diabetes mellitus, rheumatoid arthritis, irritable bowel syndrome, and gastric ulcer disease).	
Sexual dysfunction	Differential diagnosis includes: <ol style="list-style-type: none"> 1. Drugs (e.g., antihypertensives, neuroleptics, SSRIs, ethanol) 2. Diseases (e.g., depression, diabetes) 3. Psychological (e.g., performance anxiety) 	
Body-mass index (BMI)	BMI is a measure of weight adjusted for height. $\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2}$	< 18.5 underweight; 18.5–24.9 normal; 25.0–29.9 overweight; > 30.0 obese.

Intelligence quotient	<p>Stanford-Binet and Wechsler are the most famous tests of intelligence quotient (IQ). Stanford-Binet calculates IQ as mental age/chronological age \times 100. Wechsler Adult Intelligence Scale uses 11 subtests (6 verbal, 5 performance). Mean is defined at 100, with standard deviation of 15. IQ < 70 (or 2 standard deviations below the mean) is one of the criteria for diagnosis of mental retardation (MR). IQ < 40—severe MR. IQ < 20—profound MR. IQ scores are correlated with genetic factors and are highly correlated with school achievement. Intelligence tests are objective (not projective) tests.</p>	
Classical conditioning	Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).	Pavlov's classical experiments with dogs—ringing the bell provoked salivation.
Operant conditioning	<p>Learning in which a particular action is elicited because it produces a reward. Positive reinforcement—desired reward produces action (mouse presses button to get food). Negative reinforcement—removal of aversive stimulus \uparrow behavior (mouse presses button to avoid shock). Do not confuse with punishment.</p>	
Reinforcement schedules	Pattern of reinforcement determines how quickly a behavior is learned or extinguished.	
Continuous	Reward received after every response. Rapidly extinguished.	Think vending machine—stop using it if it does not deliver.
Variable ratio	Reward received after random number of responses. Slowly extinguished.	Think slot machine—continue to play even if it rarely rewards.
Transference and countertransference		
Transference	Patient projects feelings about formative or other important persons onto physician (e.g., psychiatrist = parent).	
Countertransference	Doctor projects feelings about formative or other important persons onto patient.	
Structural theory of the mind	Freud's 3 structures of the mind.	
Id	Primal urges, sex, and aggression. (I want it.)	
Superego	Moral values, conscience. (You know you can't have it.)	
Ego	Mediator between the unconscious mind and the external world. (Deals with the conflict.)	
Topographic theory of the mind	<p>Conscious—what you are aware of. Preconscious—what you are able to make conscious with effort (e.g., your phone number). Unconscious—what you are not aware of; the central goal of Freudian psychoanalysis is to make the patient aware of what is hidden in his/her unconscious.</p>	
Oedipus complex	Repressed sexual feelings of a child for the opposite-sex parent, accompanied by rivalry with same-sex parent. First described by Freud.	

► BEHAVIORAL SCIENCE—PSYCHOLOGY (*continued*)

Ego defenses	All ego defenses are automatic and unconscious reactions to psychological stress.	
Mature		
Altruism	Guilty feelings alleviated by unsolicited generosity toward others.	Mafia boss makes large donation to charity.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.
Sublimation	Process whereby one replaces an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system.	Aggressive impulses used to succeed in business ventures.
Suppression	Voluntary (unlike other defenses) withholding of an idea or feeling from conscious awareness.	Choosing not to think about the USMLE until the week of the exam.
	Mature women wear a SASH : Sublimation, Altruism, Suppression, Humor.	
Immature		
Acting out	Unacceptable feelings and thoughts are expressed through actions.	Tantrums.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.	Extreme forms can result in multiple personalities (dissociative identity disorder).
Denial	Avoidance of awareness of some painful reality.	A common reaction in newly diagnosed AIDS and cancer patients.
Displacement	Process whereby avoided ideas and feelings are transferred to some neutral person or object.	Mother yells at child because she is angry at her husband.
Fixation	Partially remaining at a more childish level of development.	Men fixating on sports games.
Identification	Modeling behavior after another person who is more powerful (though not necessarily admired).	Abused child becomes an abuser.
Isolation	Separation of feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Projection	An unacceptable internal impulse is attributed to an external source.	A man who wants another woman thinks his wife is cheating on him.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	Saying the job was not important anyway, after getting fired.
Reaction formation	Process whereby a ward-off idea or feeling is replaced by an (unconsciously derived) emphasis on its opposite.	A patient with libidinous thoughts enters a monastery.
Regression	Turning back the maturational clock and going back to earlier modes of dealing with the world.	Seen in children under stress (e.g., bed-wetting) and in patients on dialysis (e.g., crying).
Repression	Involuntary withholding of an idea or feeling from conscious awareness. The basic mechanism underlying all others.	
Splitting	Belief that people are either good or bad.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.

HIGH-YIELD PRINCIPLES IN

Biochemistry

“Biochemistry is the study of carbon compounds that crawl.”

—Mike Adams

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway. Do not spend time on hard-core organic chemistry, mechanisms, and physical chemistry. Detailed chemical structures are infrequently tested. Familiarity with the latest biochemical techniques that have medical relevance—such as enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis, Southern blotting, and PCR—is useful. Beware if you placed out of your medical school’s biochemistry class, for the emphasis of the test differs from that of many undergraduate courses. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

- ▶ High-Yield Clinical Vignettes
- ▶ Molecular
- ▶ Cellular
- ▶ Metabolism
- ▶ Laboratory Techniques
- ▶ Genetics
- ▶ Nutrition

BIOCHEMISTRY—HIGH-YIELD CLINICAL VIGNETTES

■ Full-term neonate of uneventful delivery becomes mentally retarded and hyperactive and has a musty odor.	What is the diagnosis?	PKU.
■ Stressed executive comes home from work, consumes 7 or 8 martinis in rapid succession before dinner, and becomes hypoglycemic.	What is the mechanism?	NADH increase prevents gluconeogenesis by shunting pyruvate and oxaloacetate to lactate and malate.
■ 2-year-old girl has an ↑ in abdominal girth, failure to thrive, and skin and hair depigmentation.	What is the diagnosis?	Kwashiorkor.
■ Alcoholic develops a rash, diarrhea, and altered mental status.	What is the vitamin deficiency?	Vitamin B ₃ (pellagra).
■ 51-year-old man has black spots in his sclera and has noted that his urine turns black upon standing.	What is the diagnosis?	Alkaptonuria.
■ 25-year-old male complains of severe chest pain and has xanthomas of his Achilles tendons.	What is the disease, and where is the defect?	Familial hypercholesterolemia; LDL receptor.

Chromatin structure

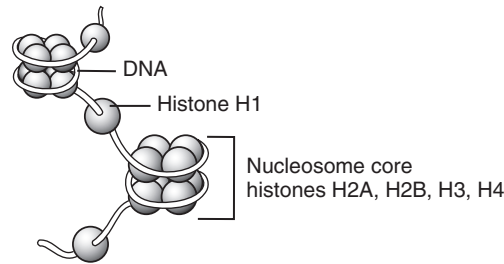
Condensed by (–) charged DNA looped twice around (+) charged H2A, H2B, H3, and H4 histone octamers (nucleosome bead). H1 ties nucleosomes together in a string (30-nm fiber).
In mitosis, DNA condenses to form mitotic chromosomes.

Think of beads on a string.

Heterochromatin
Euchromatin

Condensed, transcriptionally inactive.
Less condensed, transcriptionally active.

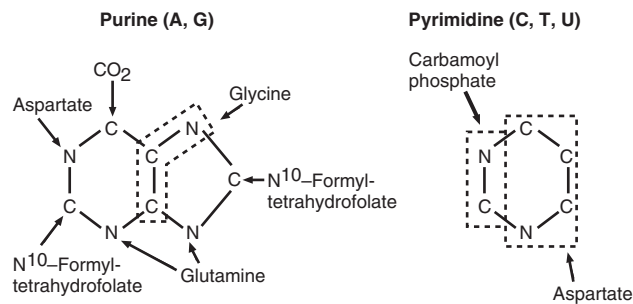
Eu = true, “truly transcribed.”



Nucleotides

Purines (A, G) have 2 rings. Pyrimidines (C, T, U) have 1 ring. Guanine has a ketone. Thymine has a methyl. Deamination of cytosine makes uracil. Uracil found in RNA; thymine in DNA. G-C bond (3 H-bonds) stronger than A-T bond (2 H-bonds). ↑ G-C content → ↑ melting temperature.

PURe As Gold: **PUR**ines.
CUT the **PY** (pie):
PYrimidines.
THYmine has a me**THY**L.



Nucleotides are linked by 3'-5' phosphodiesterase bond.

Transition vs. transversion

Transition—substituting purine for purine or pyrimidine for pyrimidine.
Transversion—substituting purine for pyrimidine or vice versa.

Trans**I**tion = **I**dentical type.
Trans**V**ersion = con**V**ersion between types.

Genetic code features

Unambiguous—each codon specifies only 1 amino acid.
Degenerate—more than 1 codon may code for same amino acid.
Commaless, nonoverlapping (except some viruses).
Universal (exceptions include mitochondria, archaeobacteria, *Mycoplasma*, and some yeasts).

► BIOCHEMISTRY—MOLECULAR (continued)

Mutations in DNA

Silent—same aa, often base change in 3rd position of codon (tRNA wobble).

Missense—changed aa (conservative—new aa is similar in chemical structure).

Nonsense—change resulting in early **stop** codon.

Frame shift—change resulting in misreading of all nucleotides downstream, usually resulting in a truncated protein.

Severity of damage: nonsense > missense > silent.

Stop the nonsense!

Prokaryotic DNA replication and DNA polymerases

Single origin of replication—continuous DNA synthesis on leading strand and discontinuous (Okazaki fragments) on lagging strand.

DNA topoisomerases create a nick in the helix to relieve supercoils.

Primase makes an RNA **primer** on which DNA polymerase III can initiate replication.

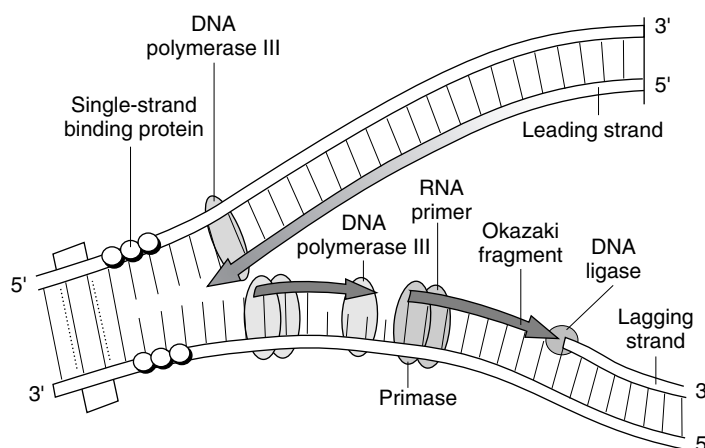
DNA polymerase III elongates the chain by adding deoxynucleotides to the 3' end until it reaches primer of preceding fragment. 3' → 5' exonuclease activity “proofreads” each added nucleotide.

DNA polymerase I degrades RNA primer.

DNA ligase seals.

DNA polymerase III has 5' → 3' synthesis and proofreads with 3' → 5' exonuclease.

DNA polymerase I excises RNA primer with 5' → 3' exonuclease.

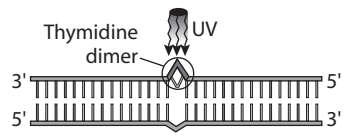
**Eukaryotic DNA polymerases**

Eukaryotic genome has multiple origins of replication. Replication begins at a consensus sequence of AT base pairs.

Eukaryotes have separate polymerases (α , β , γ , δ , ϵ) for synthesizing RNA primers, leading-strand DNA, lagging-strand DNA, mitochondrial DNA, and DNA repair.

DNA repair: single strand

Single-strand, excision repair—specific glycosylase recognizes and removes damaged base. Endonuclease makes a break several bases to the 5' side. Exonuclease removes short stretch of nucleotides. DNA polymerase fills gap. DNA ligase seals.

DNA repair defects	Xeroderma pigmentosum (skin sensitivity to UV light), ataxia-telangiectasia (x-rays), Bloom's syndrome (radiation), and Fanconi's anemia (cross-linking agents).	
Xeroderma pigmentosum	Defective excision repair such as uvr ABC endonuclease. Results in inability to repair thymidine dimers, which form in DNA when exposed to UV light. Associated with dry skin and with melanoma and other cancers.	Autosomal recessive. 
DNA/RNA/protein synthesis direction	DNA and RNA are both synthesized 5' → 3'. Remember that the 5' of the incoming nucleotide bears the triphosphate (energy source for bond). The 3' hydroxyl of the nascent chain is the target. Protein synthesis also proceeds in the 5' to 3' direction.	Imagine the incoming nucleotide bringing a gift (triphosphate) to the 3' host. “BYOP (phosphate) from 5 to 3.” Amino acids are linked N to C.
Types of RNA	mRNA is the largest type of RNA. rRNA is the most abundant type of RNA. tRNA is the smallest type of RNA.	Massive, Rampant, Tiny.
RNA polymerases		
Eukaryotes	RNA polymerase I makes rRNA . RNA polymerase II makes mRNA . RNA polymerase III makes tRNA . No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site (A-T-rich upstream sequence—TATA and CAAT). α -amanitin inhibits RNA polymerase II.	I, II, and III are numbered as their products are used in protein synthesis. α -amanitin is found in death cap mushrooms.
Prokaryotes	RNA polymerase makes all 3 kinds of RNA.	
Start and stop codons	AUG (or rarely GUG) is the mRNA initiation codon. Eukaryotes—AUG codes for methionine, which may be removed before translation is completed. Prokaryotes—the initial AUG codes for a formyl-methionine (f-met). Stop codons—UGA, UAA, UAG.	AUG in AUG urates protein synthesis. UGA = U Go Away. UAA = U Are Away. UAG = U Are Gone.

► BIOCHEMISTRY—MOLECULAR (continued)

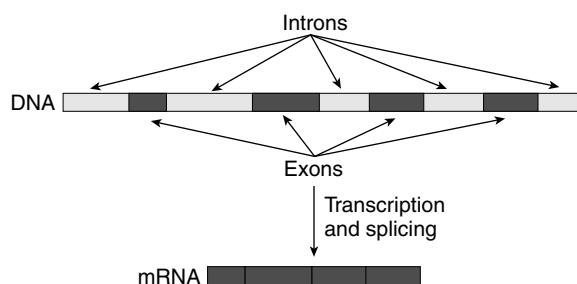
Regulation of gene expression

Promoter	Site where RNA polymerase and multiple other transcription factors bind to DNA upstream from gene locus.	Promoter mutation commonly results in dramatic ↓ in amount of gene transcribed.
Enhancer	Stretch of DNA that alters gene expression by binding transcription factors. May be located close to, far from, or even within (in an intron) the gene whose expression it regulates.	
Operator	Site where negative regulators (repressors) bind.	

Introns vs. exons

Exons contain the actual genetic information coding for protein.
Introns are intervening noncoding segments of DNA.

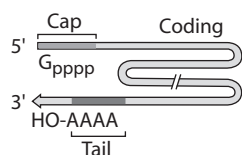
INtrons stay **IN** the nucleus, whereas **EX**ons **EX**it and are **EX**pressed.



Splicing of mRNA

Introns are precisely spliced out of 1° mRNA transcripts. A lariat-shaped intermediate is formed. Small nuclear ribonucleoprotein particles (snRNP) facilitate splicing by binding to 1° mRNA transcripts and forming spliceosomes.

RNA processing (eukaryotes)



Occurs in nucleus. After transcription:

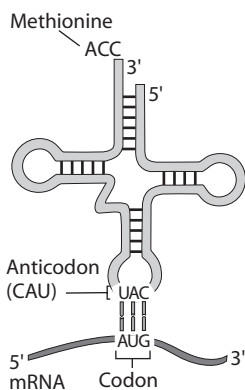
1. Capping on 5' end (7-methyl-G)
2. Polyadenylation on 3' end (≈ 200 A's)
3. Splicing out of introns

Initial transcript is called heterogeneous nuclear RNA (hnRNA).

Capped and tailed transcript is called mRNA.

Only processed RNA is transported out of the nucleus.

tRNA structure

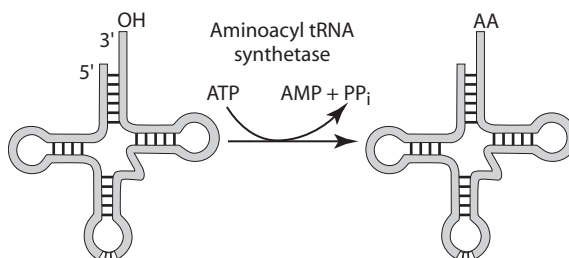


75–90 nucleotides, cloverleaf form, anticodon end is opposite 3' aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3' end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3' end of the tRNA.

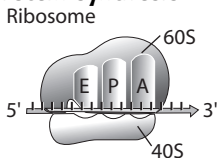
tRNA charging

Aminoacyl-tRNA synthetase (1 per aa, uses ATP) scrutinizes aa before and after it binds to tRNA. If incorrect, bond is hydrolyzed by synthetase. The aa-tRNA bond has energy for formation of peptide bond. A mischarged tRNA reads usual codon but inserts wrong amino acid.

Aminoacyl-tRNA synthetase and binding of charged tRNA to the codon are responsible for accuracy of amino acid selection.

**tRNA wobble**

Accurate base pairing is required only in the first 2 nucleotide positions of an mRNA codon, so codons differing in the 3rd “wobble” position may code for the same tRNA/amino acid.

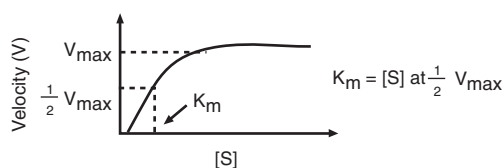
Protein synthesis

Met sits in the P site—peptidyl. The incoming amino acid binds to the A site—aminoacyl, hydrolyzing Met's bond to its tRNA while simultaneously forming a peptidyl bond between the 2 amino acids. The ribosome shifts 1 codon toward the 3' end of the mRNA, shifting the uncharged tRNA into the E position and the dipeptidyl tRNA into the P site.

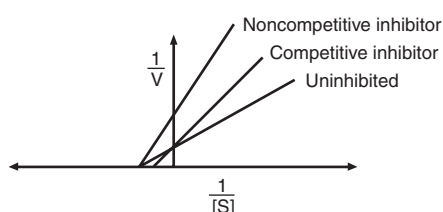
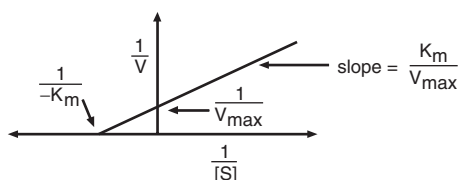
ATP—tRNA Activation (charging).
GTP—tRNA Gripping and Going places (translocation).

► BIOCHEMISTRY—CELLULAR

Enzyme kinetics



The lower the K_m , the higher the affinity.



HINT: Competitive inhibitors cross each other competitively, while noncompetitive inhibitors do not.

	Competitive inhibitors	Noncompetitive inhibitors
Resemble substrate	Yes	No
Overcome by \uparrow [S]	Yes	No
Bind active site	Yes	No
Effect on V_{\max}	Unchanged	\downarrow
Effect on K_m	\uparrow	Unchanged

Enzyme regulation methods

Enzyme concentration alteration (synthesis and/or destruction), covalent modification (e.g., phosphorylation), proteolytic modification (zymogen), allosteric regulation (e.g., feedback inhibition), and transcriptional regulation (e.g., steroid hormones).

Cell cycle phases

M (mitosis: prophase–metaphase–anaphase–telophase)

G_1 (growth)

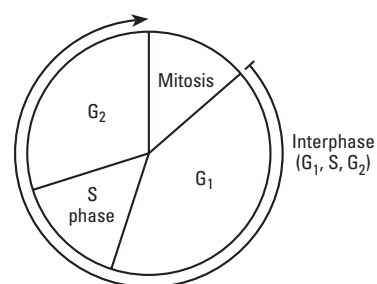
S (synthesis of DNA)

G_2 (growth)

G_0 (quiescent G_1 phase)

G_1 and G_0 are of variable duration. Mitosis is usually shortest phase. Most cells are in G_0 . Rapidly dividing cells have a shorter G_1 .

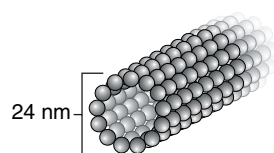
G stands for Gap or Growth; S for Synthesis.



Rough endoplasmic reticulum (RER)	RER is the site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins.	Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.
Nissl bodies	Nissl bodies (in neurons)—rough ER; not found in axon or axon hillock. Synthesize enzymes (e.g., ChAT) and peptide neurotransmitters.	
Smooth endoplasmic reticulum (SER)	SER is the site of steroid synthesis and detoxification of drugs and poisons.	Liver hepatocytes and steroid hormone-producing cells of the adrenal cortex are rich in SER.
Functions of Golgi apparatus	<ol style="list-style-type: none"> 1. Distribution center of proteins and lipids from ER to the plasma membrane, lysosomes, and secretory vesicles 2. Modifies N-oligosaccharides on asparagine 3. Adds O-oligosaccharides to serine and threonine residues 4. Proteoglycan assembly from proteoglycan core proteins 5. Sulfation of sugars in proteoglycans and of selected tyrosine on proteins 6. Addition of mannose-6-phosphate to specific lysosomal proteins, which targets the protein to the lysosome 	I-cell disease is caused by the failure of addition of mannose-6-phosphate to lysosome proteins, causing these enzymes to be secreted outside the cell instead of being targeted to the lysosome. Characterized by coarse facial features and restricted joint movement.



(Reproduced, with permission, from Junqueira L, Carneiro J. *Basic Histology*, 10th ed. New York:McGraw-Hill, 2003.)

► BIOCHEMISTRY—CELLULAR (*continued*)**Microtubule**

Cylindrical structure 24 nm in diameter and of variable length. A helical array of polymerized dimers of α - and β -tubulin (13 per circumference). Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Microtubules are also involved in slow axoplasmic transport in neurons.

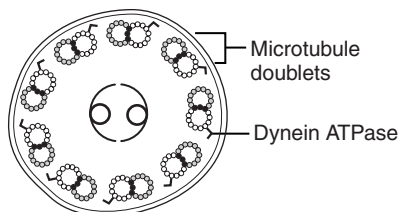
Drugs that act on microtubules:

1. Mebendazole/thiabendazole (anthelmintic)
2. Taxol (anti-breast cancer)
3. Griseofulvin (antifungal)
4. Vincristine/vinblastine (anti-cancer)
5. Colchicine (anti-gout)

Chédiak-Higashi syndrome is due to a microtubule polymerization defect resulting in \downarrow phagocytosis.

Cilia structure

9 + 2 arrangement of microtubules. Dynein is an ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.



Kartagener's syndrome is due to a dynein arm defect, resulting in immotile cilia.

Dynein = retrograde.
Kinesin = anterograde.

Plasma membrane composition

Plasma membranes contain cholesterol ($\approx 50\%$, promotes membrane stability), phospholipids ($\approx 50\%$), sphingolipids, glycolipids, and proteins. High cholesterol or long saturated fatty acid content $\rightarrow \uparrow$ melting temperature. Only noncytoplasmic side of membrane contains glycosylated lipids or proteins (i.e., the plasma membrane is an asymmetric, fluid bilayer).

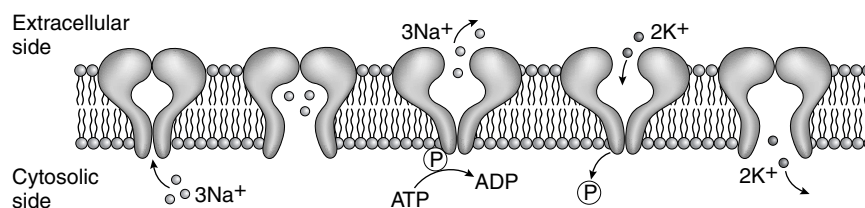
Phosphatidylcholine function

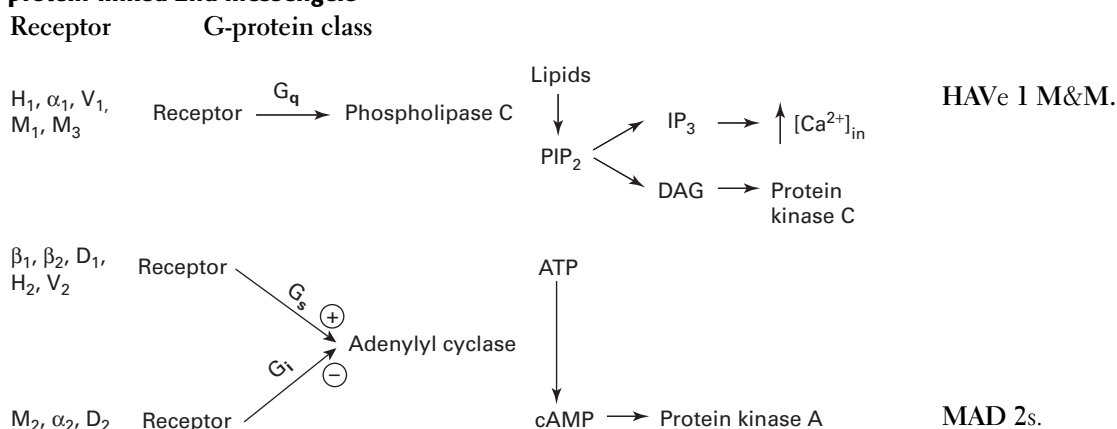
Phosphatidylcholine (lecithin) is a major component of RBC membranes, of myelin, of bile, and of surfactant (DPPC—dipalmitoyl phosphatidylcholine). Also used in esterification of cholesterol (LCAT is lecithin-cholesterol acyltransferase).

Sodium pump

Na^+ - K^+ ATPase is located in the plasma membrane with ATP site on cytoplasmic side. For each ATP consumed, 3 Na^+ go out and 2 K^+ come in. During cycle, pump is phosphorylated.

Ouabain inhibits by binding to K^+ site. Cardiac glycosides (digoxin, digitoxin) also inhibit the Na^+ - K^+ ATPase, causing \uparrow cardiac contractility.



G-protein-linked 2nd messengers**Collagen types**

Collagen is the most abundant protein in the human body. Functions to organize and strengthen extracellular matrix.

Be Cool, Read Books.

Type I (90%)—**B**one, tendon, skin, dentin, fascia, cornea, late wound repair.

Type I: **B**ONE.

Type II—**C**artilag (including hyaline), vitreous body, nucleus pulposus.

Type II: car**T**WOlage.

Type III (**R**eticulin)—skin, blood vessels, uterus, fetal tissue, granulation tissue.

Type IV—**B**asement membrane or basal lamina.

Type IV: Under the **f**loor (basement membrane).

Type X—epiphyseal plate.

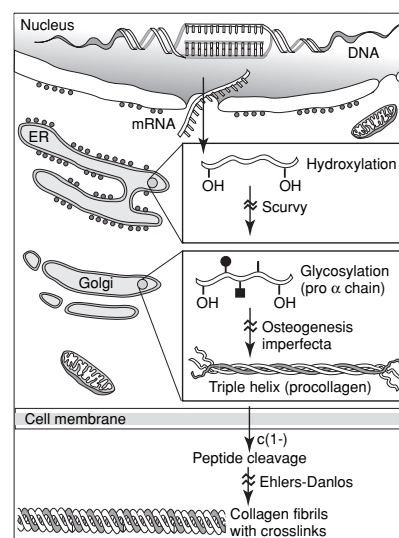
Collagen synthesis and structure

Inside fibroblasts:

1. Collagen α chains (**preprocollagen**) translated on RER—usually Gly-X-Y polypeptide (X and Y are proline, hydroxyproline, or hydroxylysine)
2. ER \rightarrow hydroxylation of specific proline and lysine residues (requires vitamin C)
3. Golgi \rightarrow glycosylation of pro- α -chain lysine residues and formation of **procollagen** (triple helix of 3 collagen α chains)
4. Procollagen molecules are exocytosed into extracellular space

Outside fibroblasts:

5. Procollagen peptidases cleave terminal regions of procollagen, transforming procollagen into insoluble **tropocollagen**
6. Many staggered tropocollagen molecules are reinforced by covalent lysine-hydroxylysine cross-linkage (by lysyl oxidase) to make **collagen fibrils**



► BIOCHEMISTRY—CELLULAR (*continued*)**Ehlers-Danlos syndrome**

Faulty collagen synthesis causing:

1. Hyperextensible skin
2. Tendency to bleed (easy bruising)
3. Hypermobility joints

10 types. Inheritance varies. Associated with berry aneurysms.

Osteogenesis imperfecta

Primarily an autosomal-dominant disorder caused by a variety of gene defects, resulting in abnormal collagen synthesis. Clinically characterized by:

1. **Multiple fractures** occurring with minimal trauma (brittle bone disease), which may occur during the birth process
2. **Blue sclerae** due to the translucency of the connective tissue over the choroid
3. Hearing loss (abnormal middle ear bones)
4. Dental imperfections due to lack of dentition

May be confused with child abuse.

Type II is fatal in utero and in the neonatal period.

Incidence is 1:10,000.

Immunohistochemical stains**Stain**

Vimentin

Desmin

Cytokeratin

Glial fibrillary acid proteins (GFAP)

Neurofilaments

Cell type

Connective tissue

Muscle

Epithelial cells

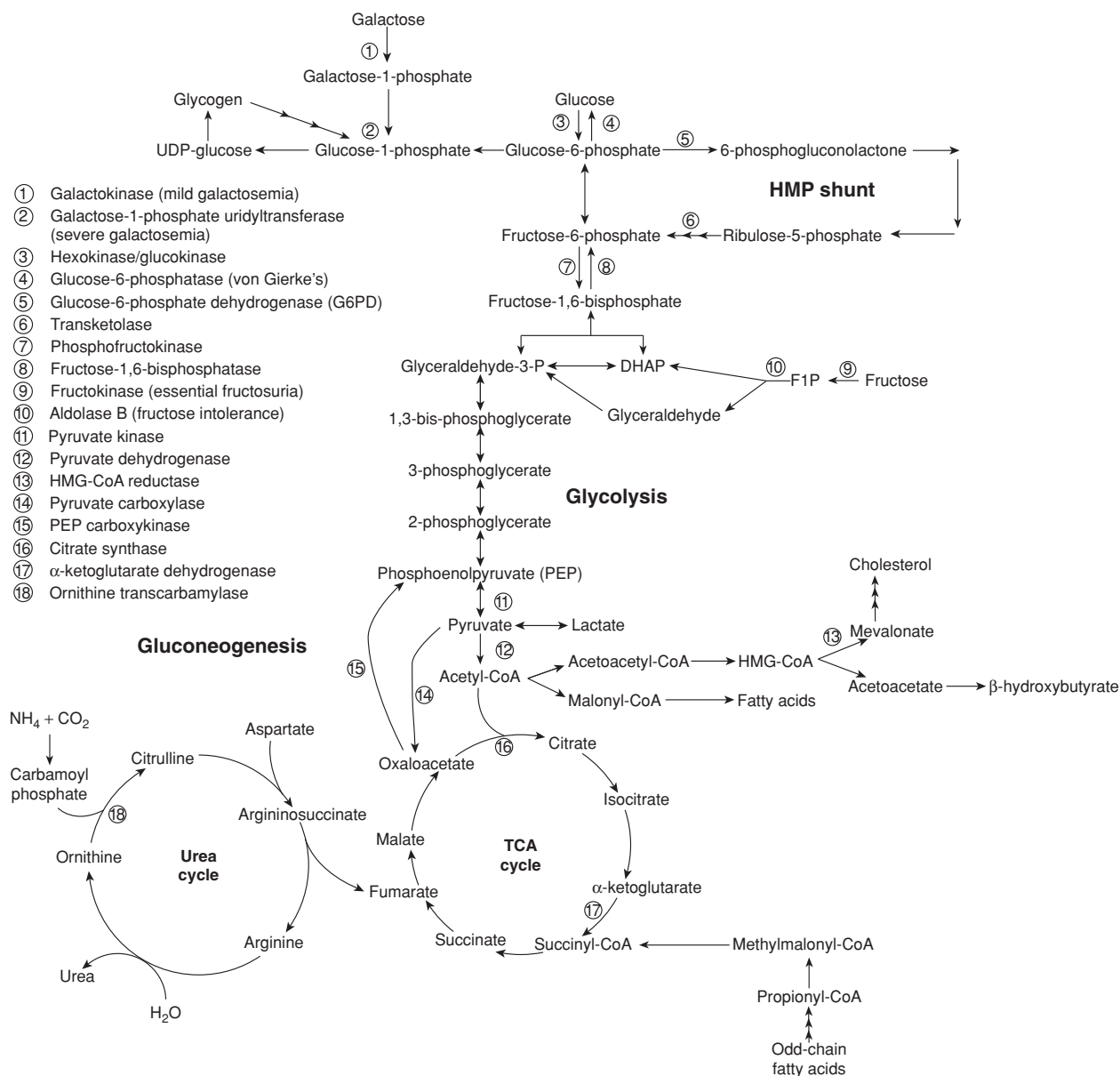
Neuroglia

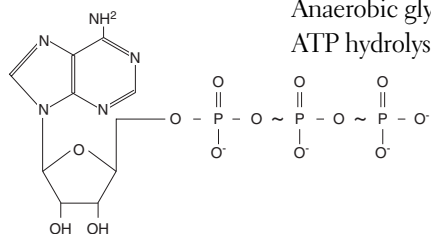
Neurons

Metabolism sites

Mitochondria	Fatty acid oxidation (β -oxidation), acetyl-CoA production, Krebs cycle.
Cytoplasm	Glycolysis, fatty acid synthesis, HMP shunt, protein synthesis (RER), steroid synthesis (SER).
Both	Gluconeogenesis, urea cycle, heme synthesis.

Summary of pathways



► BIOCHEMISTRY—METABOLISM (*continued*)**ATP**

Base (adenine), ribose, 3 phosphoryls. 2 phosphoanhydride bonds, 7 kcal/mol each.

Aerobic metabolism of glucose produces 38 ATP via malate shuttle, 36 ATP via G3P shuttle.

Anaerobic glycolysis produces only 2 net ATP per glucose molecule.

ATP hydrolysis can be coupled to energetically unfavorable reactions.

Activated carriers

Phosphoryl (ATP).

Electrons (NADH, NADPH, FADH₂).

Acyl (coenzyme A, lipoamide).

CO₂ (biotin).

1-carbon units (tetrahydrofolates).

CH₃ groups (SAM).

Aldehydes (TPP).

Glucose (UDP-glucose).

Choline (CDP-choline).

S-adenosyl-methionine

ATP + methionine → **SAM**. SAM transfers methyl units to a wide variety of acceptors (e.g., in synthesis of phosphocreatine, a high-energy phosphate active in muscle ATP production). Regeneration of methionine (and thus SAM) is dependent on vitamin B₁₂.

SAM the methyl donor man.

Signal molecule precursors

ATP → cAMP via adenylate cyclase.

GTP → cGMP via guanylate cyclase.

Glutamate → GABA via glutamate decarboxylase (requires vitamin B₆).

Choline → ACh via choline acetyltransferase (ChAT).

Arachidonate → prostaglandins, thromboxanes, leukotrienes via cyclooxygenase/lipoxygenase.

Fructose-6-P → fructose-1,6-bis-P via phosphofructokinase (PFK), the rate-limiting enzyme of glycolysis.

1,3-BPG → 2,3-BPG via bisphosphoglycerate mutase.

Universal electron acceptors

Nicotinamides (NAD⁺, NADP⁺) and flavin nucleotides (FAD⁺).

NAD⁺ is generally used in **catabolic** processes to carry reducing equivalents away as NADH.

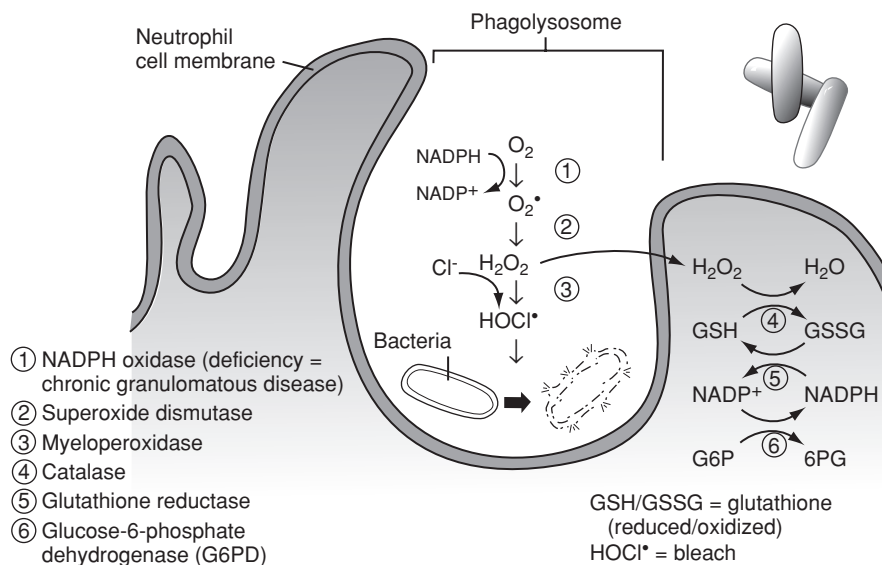
NADPH is used in **anabolic** processes (steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt.

NADPH is used in:

1. Anabolic processes
2. Respiratory burst
3. P-450

Oxygen-dependent respiratory burst

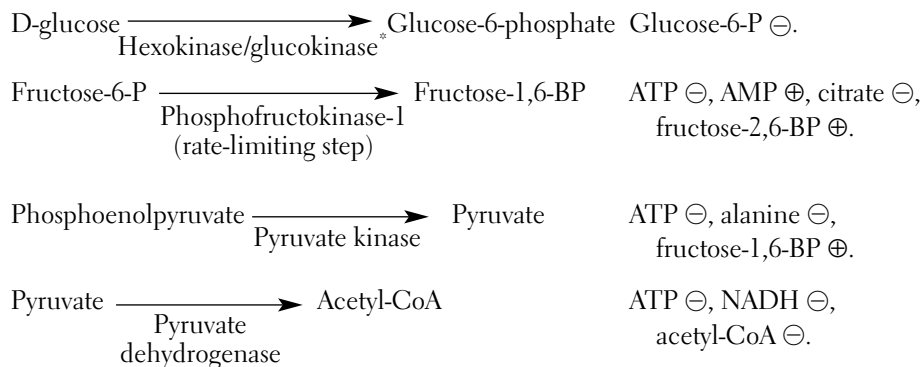


Hexokinase vs. glucokinase

Hexokinase is found throughout body.
Glucokinase is primarily found in the Liver
(lower affinity [$\uparrow K_m$] but higher capacity [$\uparrow V_{max}$]).

Only hexokinase is feedback inhibited by G6P.
Glucokinase phosphorylates excess glucose (e.g., after a meal) to sequester it in the liver as G6P.

Glycolysis regulation, irreversible enzymes



* Glucokinase in liver; hexokinase in all other tissues.

Glycolytic enzyme deficiency

Hexokinase, glucose phosphate isomerase, aldolase, triosephosphate isomerase, phosphate glycerate kinase, enolase, and pyruvate kinase deficiencies are associated with hemolytic anemia.

RBCs metabolize glucose anaerobically (no mitochondria) and thus depend solely on glycolysis.

► BIOCHEMISTRY—METABOLISM (*continued*)**Pyruvate dehydrogenase complex**

The complex contains 3 enzymes that require 5 cofactors (the first 4 B vitamins plus lipoic acid):

1. Pyrophosphate (B_1 , thiamine; TPP)
2. FAD (B_2 , riboflavin)
3. NAD (B_3 , niacin)
4. CoA (B_5 , pantothenate)
5. Lipoic acid

Reaction: $\text{pyruvate} + \text{NAD}^+ + \text{CoA} \rightarrow \text{acetyl-CoA} + \text{CO}_2 + \text{NADH}$.

Activated by exercise:

↑ NAD^+/NADH ratio

↑ ADP

↑ Ca^{2+}

The complex is similar to the α -ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action).

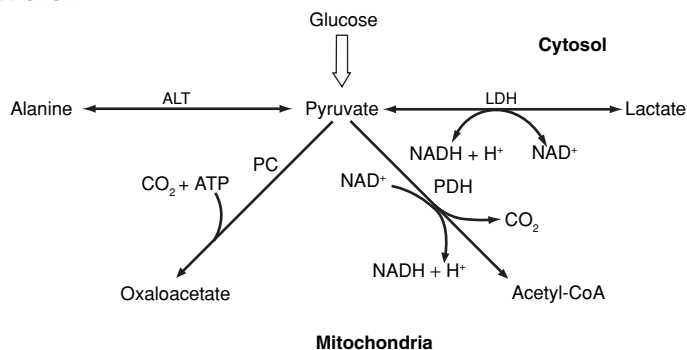
Pyruvate dehydrogenase deficiency

Causes backup of substrate (pyruvate and alanine), resulting in lactic acidosis. Can be seen in alcoholics due to B_1 deficiency.

Findings: neurologic defects.

Treatment: ↑ intake of ketogenic nutrients (e.g., high fat content or ↑ lysine and leucine).

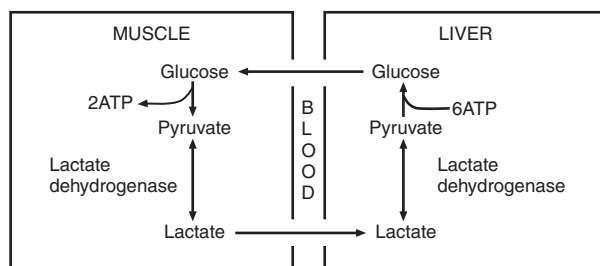
Lysine and Leucine—the only purely ketogenic amino acids.

Pyruvate metabolism

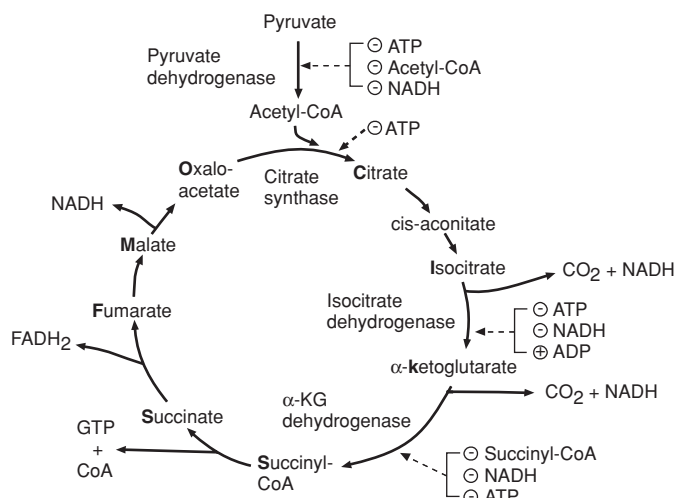
6 ATP equivalents are needed to generate glucose from pyruvate.

Alanine serves as carrier of amino groups from muscle to liver.

Oxaloacetate can be used to replenish TCA cycle or in gluconeogenesis.

Cori cycle

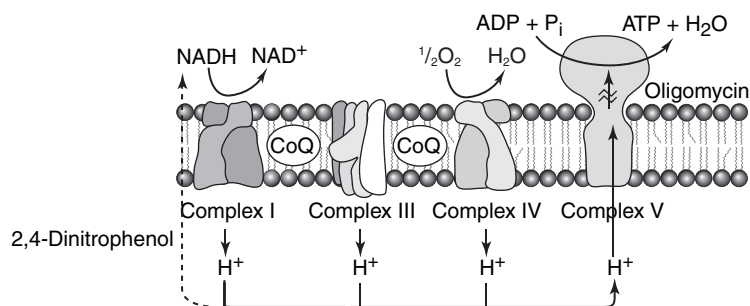
Transfers excess reducing equivalents from RBCs and muscle to liver, allowing muscle to function anaerobically (net 2 ATP).

TCA cycle

Produces 3 NADH, 1 FADH₂,
2 CO₂, 1 GTP per acetyl-
CoA = 12 ATP/acetyl-CoA
(2× everything per glucose)

α-ketoglutarate dehydrogenase
complex requires same
cofactors as the pyruvate
dehydrogenase complex.

Can I Keep Selling Sex
For Money, Officer?

Electron transport chain and oxidative phosphorylation

Electron transport
chain

Oxidative
phosphorylation
poisons

1 NADH → 3 ATP; 1 FADH₂ → 2 ATP.

1. Electron transport inhibitors (rotenone, antimycin A, CN⁻, CO) directly inhibit electron transport, causing a ↓ of proton gradient and block of ATP synthesis.
2. ATPase inhibitor (oligomycin) directly inhibits mitochondrial ATPase, causing an ↑ of proton gradient, but no ATP is produced because electron transport stops.
3. Uncoupling agents (2,4-DNP) ↑ permeability of membrane, causing a ↓ of proton gradient and ↑ O₂ consumption. ATP synthesis stops. Electron transport continues.

► BIOCHEMISTRY—METABOLISM (*continued*)**Gluconeogenesis, irreversible enzymes**

Pyruvate carboxylase In mitochondria. Pyruvate → oxaloacetate. Requires biotin, ATP.
Activated by acetyl-CoA.

PEP carboxykinase In cytosol. Oxaloacetate → phosphoenolpyruvate. Requires GTP.

Fructose-1,6-bisphosphatase In cytosol. Fructose-1,6-bisphosphate → fructose-6-P.

Glucose-6-phosphatase In cytosol. Glucose-6-P → glucose.

**Pathway Produces
Fresh Glucose.**

Above enzymes found only in liver, kidney, intestinal epithelium. Muscle cannot participate in gluconeogenesis.

Hypoglycemia is caused by a deficiency of the key gluconeogenic enzymes listed above (e.g., von Gierke's disease, which is caused by a lack of glucose-6-phosphatase in the liver).

Pentose phosphate pathway (HMP shunt)

Produces ribose-5-P from G6P for nucleotide synthesis.

Produces NADPH from NADP⁺ for fatty acid and steroid biosynthesis and for maintaining reduced glutathione inside RBCs.

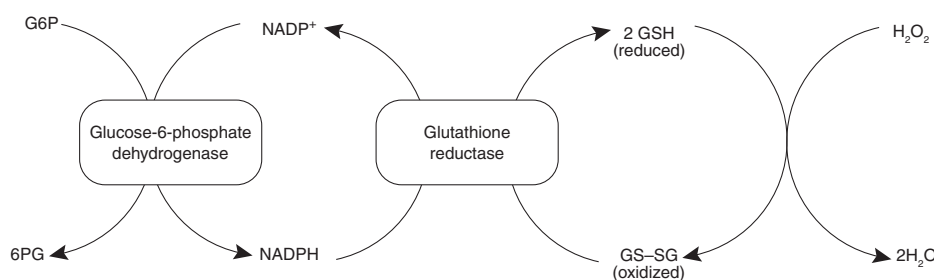
All reactions of this pathway occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex—all sites of fatty acid or steroid synthesis.

Glucose-6-phosphate dehydrogenase deficiency

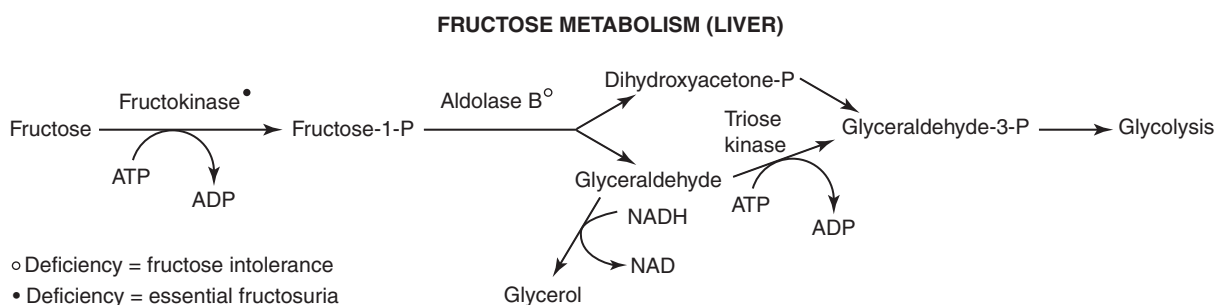
G6PD is a rate-limiting enzyme in HMP shunt (which yields NADPH). NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to **hemolytic anemia** due to poor RBC defense against oxidizing agents (fava beans, sulfonamides, primaquine) and antituberculosis drugs.

G6PD deficiency is more prevalent among blacks.
Heinz bodies—altered Hemoglobin precipitates within RBCs.
X-linked recessive disorder.

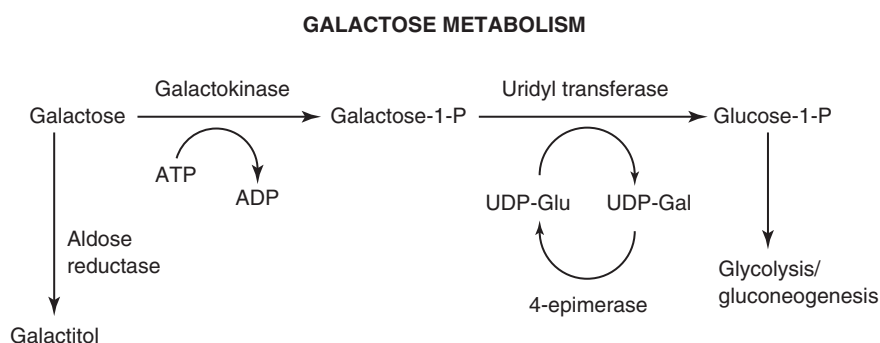


Disorders of fructose metabolism

Fructose intolerance	Hereditary deficiency of aldolase B (recessive). Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting. Treatment: must ↓ intake of both fructose and sucrose (glucose + fructose).
Essential fructosuria	Involves a defect in fructokinase and is a benign, asymptomatic condition. Symptoms: fructose appears in blood and urine.

**Disorders of galactose metabolism**

Galactosemia	Absence of galactose-1-phosphate uridylyltransferase. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol) rather than absence of an essential compound. Symptoms: cataracts, hepatosplenomegaly, mental retardation. Treatment: exclude galactose and lactose (galactose + glucose) from diet.
Galactokinase deficiency	Causes galactosemia and galactosuria, galactitol accumulation if galactose is present in diet.

**Lactase deficiency**

Age-dependent and/or hereditary lactose intolerance (blacks, Asians).
Symptoms: bloating, cramps, osmotic diarrhea.
Treatment: avoid milk or add lactase pills to diet.

Essential amino acids

Ketogenic: Leu, Lys.
Glucogenic/ketogenic: Ile, Phe, Trp.
Glucogenic: Met, Thr, Val, Arg, His.

All essential amino acids:
PriVaTe TIM HALL.
Arg and His are required during periods of growth.

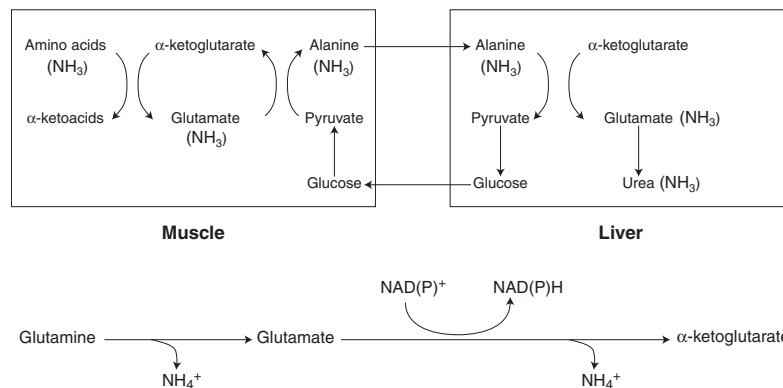
► BIOCHEMISTRY—METABOLISM (*continued*)**Acidic and basic amino acids**

At body pH (7.4), acidic amino acids Asp and Glu are negatively charged; basic amino acids Arg and Lys are positively charged. Basic amino acid His at pH 7.4 has no net charge.

Arginine is the most basic amino acid. Arg and Lys are found in high amounts in histones, which bind to negatively charged DNA.

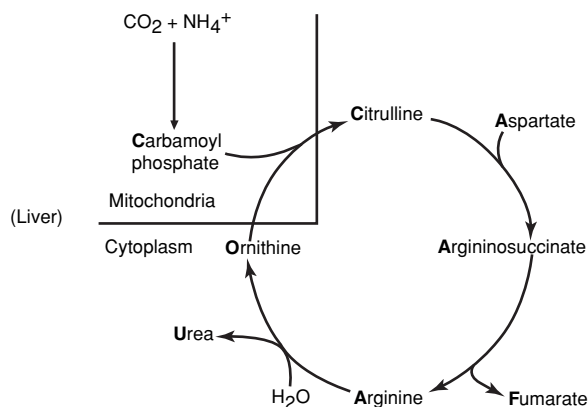
Asp = aspartic ACID, Glu = glutamic ACID.

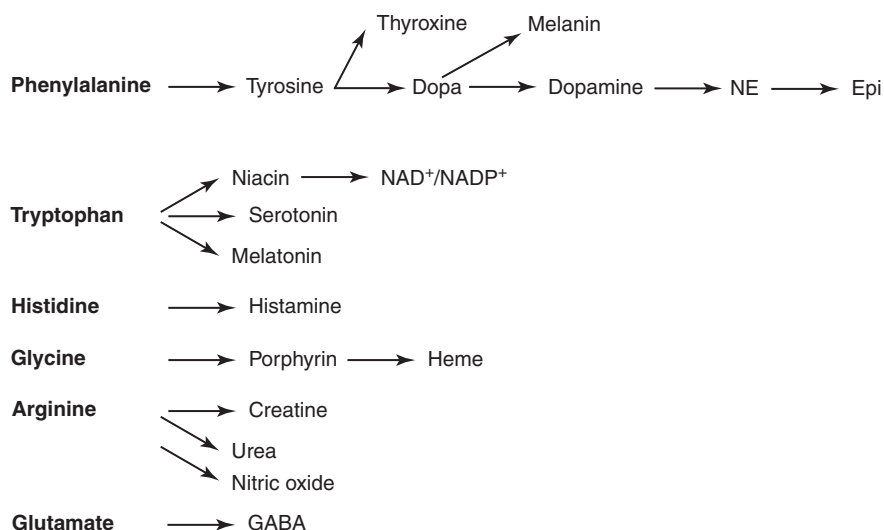
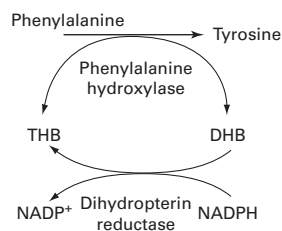
Arg and Lys have an extra NH_3 group.

Transport of ammonium by alanine and glutamine**Urea cycle**

Degrades amino acids into amino groups. Accounts for 90% of nitrogen in urine. Urea cycle occurs in the liver; carbamoyl phosphate incorporation occurs in the mitochondria; the remaining steps occur in the cytosol.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.



Amino acid derivatives**Phenylketonuria**

Normally, phenylalanine is converted into tyrosine (nonessential aa). In PKU, there is ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor. Tyrosine becomes essential and phenylalanine builds up, leading to excess phenylketones in urine.

Findings: mental retardation, growth retardation, fair skin, eczema, musty body odor.

Treatment: ↓ phenylalanine (contained in aspartame, e.g., NutraSweet) and ↑ tyrosine in diet.

Screened for at birth.

Phenylketones—phenylacetate, phenyllactate, and phenylpyruvate.

Autosomal-recessive disease.

Incidence ≈ 1:10,000.

Disorder of **aromatic** amino acid metabolism → musty body **odor**.

Alkaptonuria

Congenital deficiency of homogentisic acid oxidase in the degradative pathway of tyrosine. Resulting alkapton bodies cause urine to turn black on standing. Also, the connective tissue is dark. Benign disease. May have debilitating arthralgias.

Albinism

Congenital deficiency of either of the following:

1. Tyrosinase (inability to synthesize melanin from tyrosine)
2. Defective tyrosine transporters (↓ amounts of tyrosine and thus melanin)

Can result from a lack of migration of neural crest cells.

Lack of melanin results in an ↑ risk of skin cancer.

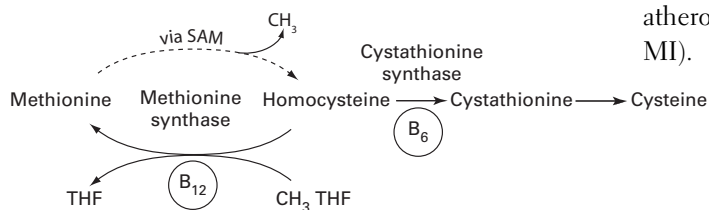
► BIOCHEMISTRY–METABOLISM (*continued*)**Homocystinuria**

3 forms:

1. Cystathionine synthase deficiency (treatment: ↓ Met and ↑ Cys in diet)
2. ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ vitamin B₆ in diet)
3. Methionine synthase deficiency

Results in excess homocysteine in the urine. Cysteine becomes essential.

Can cause mental retardation, osteoporosis, tall stature, kyphosis, lens subluxation (downward and inward), and atherosclerosis (stroke and MI).

**Cystinuria**

Common (1:7000) inherited defect of renal tubular amino acid transporter for Cystine, Ornithine, Lysine, and Arginine in kidneys. Excess cystine in urine can lead to the precipitation of cystine kidney stones.

COLA.

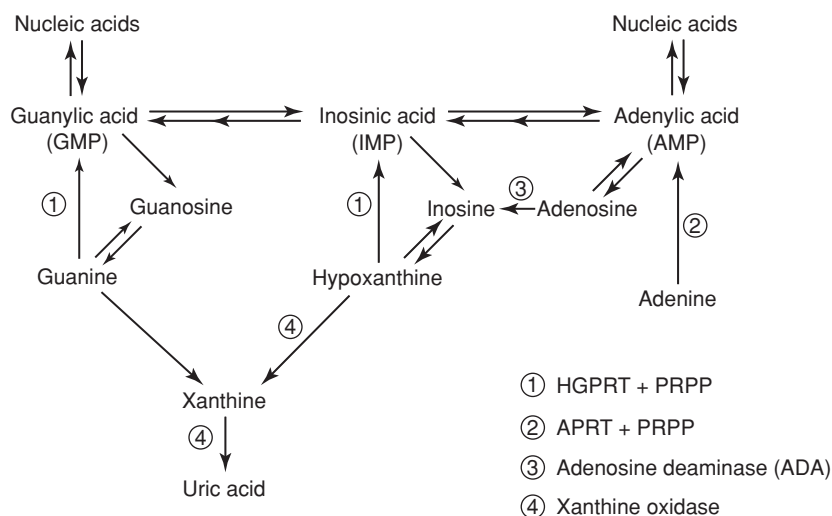
Treat with acetazolamide to alkalinize the urine.

Maple syrup urine disease

Blocked degradation of **branched** amino acids (Ile, Val, Leu) due to ↓ α-ketoacid dehydrogenase. Causes ↑ α-ketoacids in the blood, especially Leu. Causes severe CNS defects, mental retardation, and death.

Urine smells like maple syrup. **I Love Vermont** maple syrup.

Purine salvage deficiencies



Adenosine
deaminase
deficiency

ADA deficiency can cause SCID. Excess ATP and dATP imbalances nucleotide pool via feedback inhibition of ribonucleotide reductase. This prevents DNA synthesis and thus ↓ lymphocyte count. 1st disease to be treated by experimental human gene therapy.

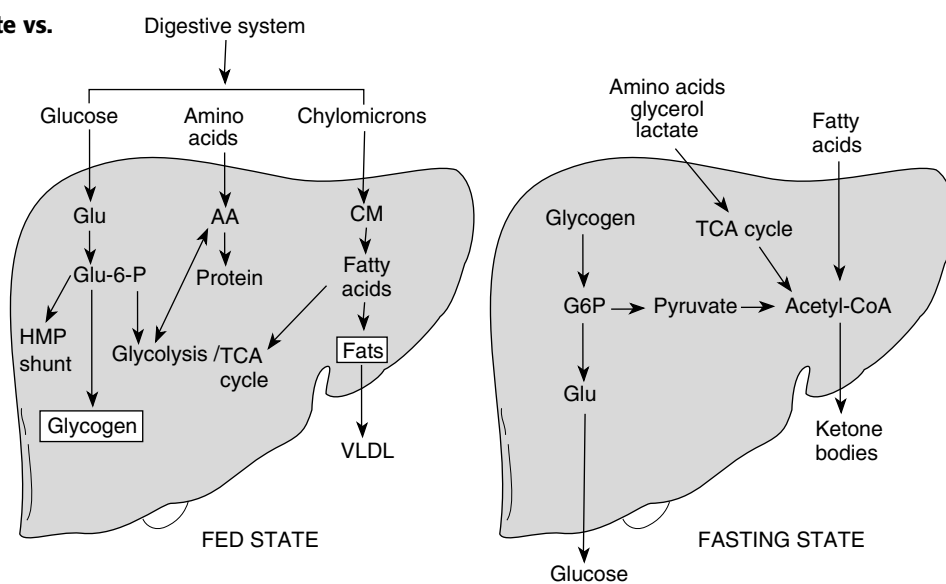
SCID—severe combined (T and B) immunodeficiency disease. **SCID** happens to **kids** (remember “bubble boy”).

Lesch-Nyhan
syndrome

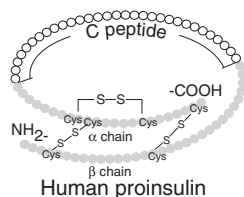
Purine salvage problem owing to absence of HGPRTase, which converts hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP). X-linked recessive. Results in excess uric acid production. Findings: retardation, self-mutilation, aggression, hyperuricemia, gout, and choreoathetosis.

LNS—Lacks Nucleotide Salvage (purine).

Liver: fed state vs. fasting state



In the **PH**asting state,
PHosphorylate.

► BIOCHEMISTRY—METABOLISM (*continued*)**Insulin**

Made in β cells of pancreas. Required for adipose and skeletal muscle uptake of glucose.

GLUT2 receptors are found in β cells and GLUT4 in muscle and fat. Insulin inhibits glucagon release by α cells of pancreas.

Serum C-peptide is not present with exogenous insulin intake.

Anabolic effects of insulin:

1. \uparrow glucose transport
2. \uparrow glycogen synthesis and storage
3. \uparrow triglyceride synthesis and storage
4. \uparrow Na retention (kidneys)
5. \uparrow protein synthesis (muscles)

Insulin moves glucose **Into** cells.
BRICK L (don't need insulin for glucose uptake):

Brain
RBCs
Intestine
Cornea
Kidney
Liver

Insulin vs. glucagon

Glucagon phosphorylates stuff \rightarrow turns glycogen synthase OFF and phosphorylase ON.
Insulin dephosphorylates stuff \rightarrow turns glycogen synthase ON and phosphorylase OFF.

Glycogen storage diseases

12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.

Type I

Von Gierke's disease—glucose-6-phosphatase deficiency.

The liver becomes a muscle.
(Think about it.)

Findings: severe fasting hypoglycemia, $\uparrow\uparrow$ glycogen in liver, hepatomegaly, \uparrow blood lactate.

Type II

Pompe's disease—lysosomal α -1,4-glucosidase deficiency.

Pompe's trashes the **Pump**
(heart, liver, and muscle).

Findings: cardiomegaly and systemic findings, leading to early death.

Type III

Cori's disease—deficiency of debranching enzyme α -1,6-glucosidase.

Findings: milder form of type I with normal blood lactate levels.

Type V

McArdle's disease—skeletal muscle glycogen phosphorylase deficiency.

McArdle's: **Muscle**.

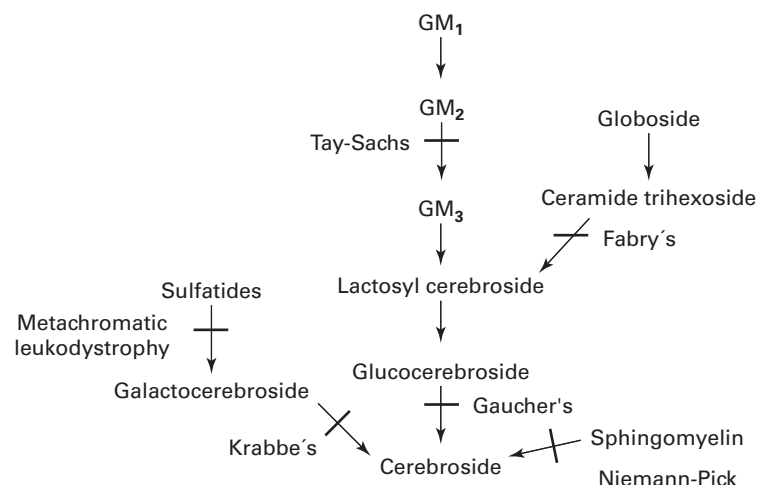
Findings: \uparrow glycogen in muscle but cannot break it down, leading to painful cramps, myoglobinuria with strenuous exercise.

Very Poor Carbohydrate Metabolism.

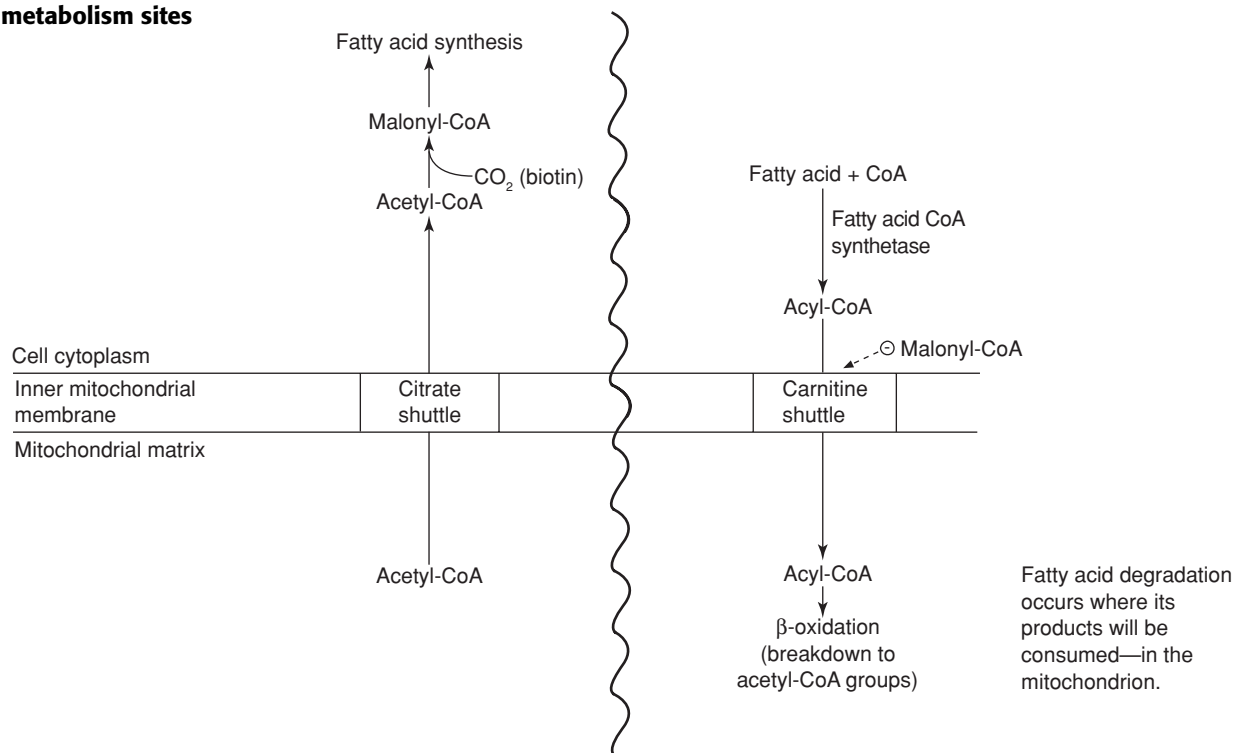
Lysosomal storage diseases

Each is caused by a deficiency in one of the many lysosomal enzymes.

Disease	Findings	Deficient enzyme	Accumulated substrate	Inheritance
Fabry's disease	Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular/renal disease	α -galactosidase A	Ceramide trihexoside	XR
Gaucher's disease	Hepatosplenomegaly, aseptic necrosis of femur, bone crises, Gaucher's cells (macrophages)	β -glucocerebrosidase	Glucocerebroside	AR
Niemann-Pick disease	Progressive neurodegeneration, hepatosplenomegaly, cherry-red spot (on macula)	Sphingomyelinase	Sphingomyelin	AR
Tay-Sachs disease	Progressive neurodegeneration, developmental delay, cherry-red spot, lysosomes with onion skin	Hexosaminidase A	GM ₂ ganglioside	AR
Krabbe's disease	Peripheral neuropathy, developmental delay, optic atrophy	β -galactosidase	Galactocerebroside	AR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia	Arylsulfatase A	Cerebroside sulfate	AR
Hurler's syndrome	Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly	α -L-iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter's syndrome	Mild Hurler's + aggressive behavior, no corneal clouding	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR



No man picks (Niemann-Pick)
his nose with his **sphinger**
(**sphingomyelinase**).
Tay-SaX (Tay-Sachs)
lacks he**X**osaminidase.
Hunters aim for the **X**
(**X**-linked recessive).

► BIOCHEMISTRY—METABOLISM (*continued*)**Fatty acid metabolism sites****Ketone bodies**

In liver: fatty acid and amino acids \rightarrow acetoacetate + β -hydroxybutyrate (to be used in muscle and brain). Ketone bodies found in prolonged starvation and diabetic ketoacidosis. Excreted in urine. Made from HMG-CoA. Ketone bodies are metabolized by the brain to 2 molecules of acetyl-CoA.

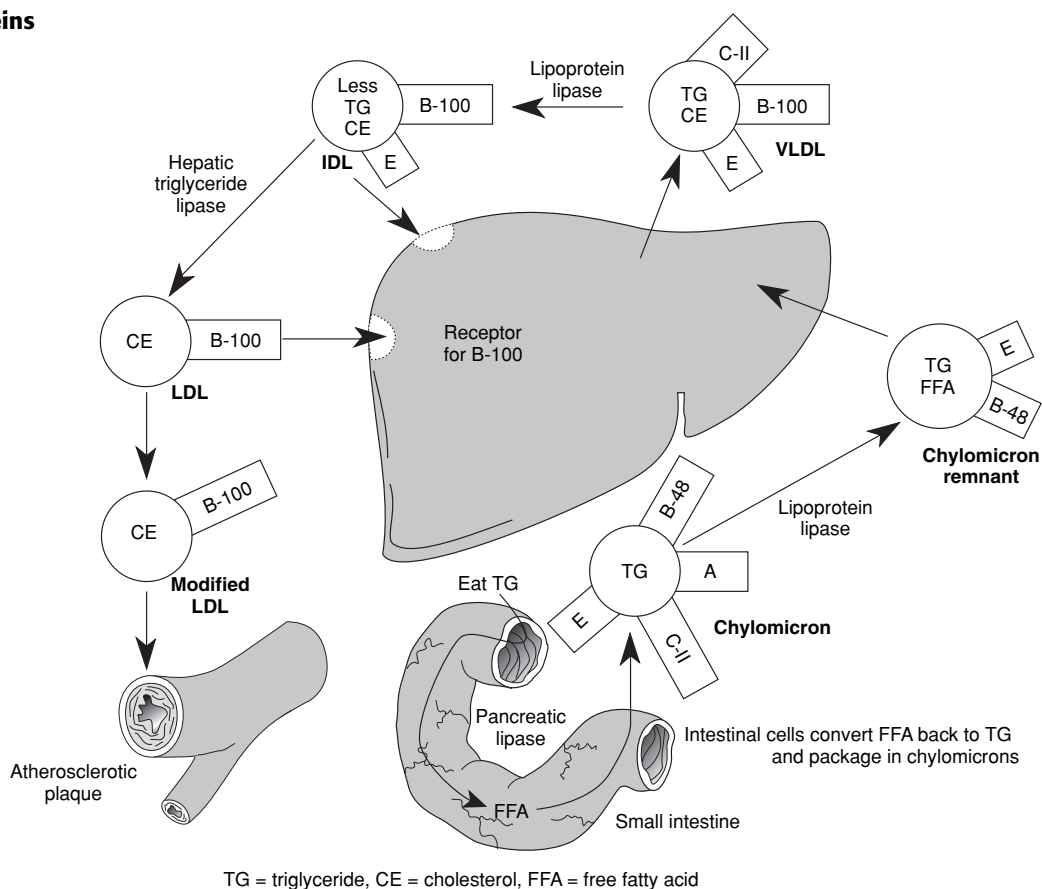
Breath smells like acetone (fruity odor). Urine test for ketones does not detect β -hydroxybutyrate (favored by high redox state).

Cholesterol synthesis

Rate-limiting step is catalyzed by HMG-CoA reductase, which converts HMG-CoA to mevalonate. $\frac{2}{3}$ of plasma cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT).

Lovastatin inhibits HMG-CoA reductase.

Lipoproteins



Pancreatic lipase—degradation of dietary TG in small intestine.

Lipoprotein lipase—degradation of TG circulating in chylomicrons and VLDLs.

Hepatic TG lipase—degradation of TG remaining in IDL.

Hormone-sensitive lipase—degradation of TG stored in adipocytes.

Major apolipoproteins

A-I—Activates LCAT.

B-100—Binds to LDL receptor.

C-II—Cofactor for lipoprotein lipase.

E—Mediates Extra (remnant) uptake.

► **BIOCHEMISTRY—METABOLISM** (*continued*)

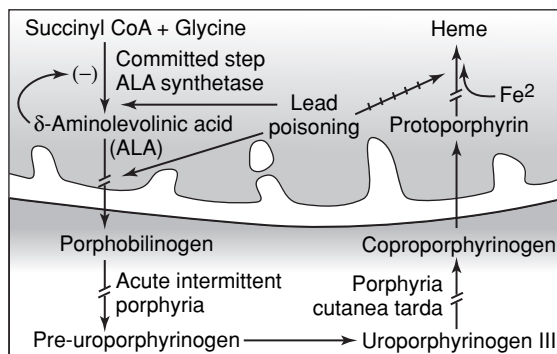
Lipoprotein functions	Lipoproteins are composed of varying proportions of cholesterol, triglycerides, and phospholipids.		
	Function and route	Apolipoproteins	
Chylomicron	Delivers dietary triglycerides to peripheral tissues and dietary cholesterol to liver. Secreted by intestinal epithelial cells. Excess causes pancreatitis, lipemia retinalis, and eruptive xanthomas.	B-48 mediates secretion. A's are used for formation of new HDL. C-II activates lipoprotein lipase. E mediates remnant uptake by liver.	
VLDL	Delivers hepatic triglycerides to peripheral tissues. Secreted by liver. Excess causes pancreatitis.	B-100 mediates secretion. C-II activates lipoprotein lipase. E mediates remnant uptake by liver.	
IDL	Formed in the degradation of VLDL. Delivers triglycerides and cholesterol to liver, where they are degraded to LDL.		
LDL	Delivers hepatic cholesterol to peripheral tissues. Formed by lipoprotein lipase modification of VLDL in the peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. Excess causes atherosclerosis, xanthomas, and arcus corneae.	B-100 mediates binding to cell surface receptor for endocytosis.	
HDL	Mediates centripetal transport of cholesterol (reverse cholesterol transport, from periphery to liver). Acts as a repository for apoC and apoE (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine.	A's help form HDL structure. A-I in particular activates LCAT (which catalyzes esterification of cholesterol). CETP mediates transfer of cholesteryl esters to other lipoprotein particles.	
	LDL and HDL carry most cholesterol. LDL transports cholesterol from liver to tissue; HDL transports it from periphery to liver.	HDL is Healthy . LDL is Lousy .	

Familial dyslipidemias

Type	Increased	Elevated blood levels	Pathophysiology
I—hyperchylomicronemia	Chylomicrons	TG, cholesterol	Lipoprotein lipase deficiency or altered apolipoprotein C-II
IIa—hypercholesterolemia	LDL	Cholesterol	↓ LDL receptors
IIb—combined hyperlipidemia	LDL, VLDL	TG, cholesterol	Hepatic overproduction of VLDL
III—dysbetalipoproteinemia	IDL, VLDL	TG, cholesterol	Altered apolipoprotein E
IV—hypertriglyceridemia	VLDL	TG	Hepatic overproduction of VLDL
V—mixed hypertriglyceridemia	VLDL, chylomicrons	TG, cholesterol	↑ production/↓ clearance of VLDL and chylomicrons

Heme synthesis

Underproduction of heme causes microcytic hypochromic anemia. Accumulation of intermediates causes porphyrias.

**Porphyrias**

Lead poisoning

Inhibits ferrochelatase and ALA dehydratase.

Coproporphyrin and ALA accumulate in urine.

Acute intermittent porphyria

Deficiency in uroporphyrinogen I synthetase.

Porphobilinogen and δ -ALA accumulate in urine.

Porphyria cutanea tarda

Deficiency in uroporphyrinogen decarboxylase.

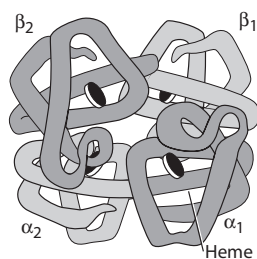
Uroporphyrin accumulates in urine (tea-colored).

Photosensitivity.

Symptoms = **5 P's**: Painful abdomen, Pink urine, Polyneuropathy, Psychological disturbances, Precipitated by drugs.

Heme catabolism

Heme is scavenged from RBCs and Fe^{2+} is reused. Heme \rightarrow biliverdin \rightarrow bilirubin (sparingly water soluble, toxic to CNS, transported by albumin). Bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. In the intestine it is processed into its excreted form. Some urobilinogen, an intestinal intermediate, is reabsorbed into blood and excreted as urobilin into urine.

Hemoglobin

Hemoglobin is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:

1. T (taut) form has low affinity for O_2 .
2. R (relaxed) form has high affinity for O_2 (300 \times). Hemoglobin exhibits positive cooperativity and negative allostery (accounts for the sigmoid-shaped O_2 dissociation curve for hemoglobin), unlike myoglobin.

Carbon monoxide has 200 \times greater affinity than O_2 for hemoglobin.

Hemoglobin structure regulation

$\uparrow \text{Cl}^-$, H^+ , CO_2 , 2,3-BPG, and temperature favor T form over R form (shifts dissociation curve to right, leading to $\uparrow \text{O}_2$ unloading).

When you're **Relaxed**, you do your job better (carry O_2). Fetal hemoglobin (2 α and 2 γ subunits) has lower affinity for 2,3-BPG than adult hemoglobin (HbA) and thus has higher affinity for O_2 .

► BIOCHEMISTRY–METABOLISM (*continued*)

Methemoglobinemia	Iron in hemoglobin is in a reduced state (ferrous, Fe^{2+}). Methemoglobin is an oxidized form of hemoglobin (ferric, Fe^{3+}) that does not bind O_2 as readily but has \uparrow affinity for CN^- .	Administer nitrites in cyanide poisoning to oxidize hemoglobin to methemoglobin form. Treat toxic levels of METH emoglobin with METH ylene blue.
CO_2 transport in blood	CO_2 binds to amino acids in globin chain (at N terminus) but not to heme. CO_2 binding favors T (taut) form of hemoglobin (and thus promotes O_2 unloading).	CO_2 must be transported from tissue to lungs, the reverse of O_2 (occurs primarily in the form of bicarbonate).

Polymerase chain reaction (PCR)

Molecular biology laboratory procedure that is used to synthesize many copies of a desired fragment of DNA.

Steps:

1. DNA is denatured by heating to generate 2 separate strands
2. During cooling, excess premade DNA primers anneal to a specific sequence on each strand to be amplified
3. Heat-stable DNA polymerase replicates the DNA sequence following each primer

These steps are repeated multiple times for DNA sequence amplification.

Molecular biology techniques

Southern blot

A DNA sample is electrophoresed on a gel and then transferred to a filter. The filter is then soaked in a denaturant and subsequently exposed to a labeled DNA probe that recognizes and anneals to its complementary strand. The resulting double-stranded labeled piece of DNA is visualized when the filter is exposed to film.

SNoW DRoP:

Southern = DNA

Northern = RNA

Western = Protein

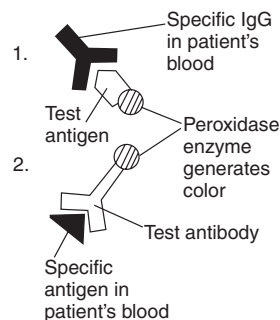
Northern blot

Similar technique, except that Northern blotting involves radioactive DNA probe binding to sample **RNA**.

Western blot

Sample protein is separated via gel electrophoresis and transferred to a filter. Labeled antibody is used to bind to relevant **protein**.

Enzyme-linked immunosorbent assay (ELISA)



A rapid immunologic technique testing for **antigen-antibody** reactivity.

Patient's blood sample is probed with either

1. Test antigen (coupled to color-generating enzyme)—to see if immune system recognizes it; or
2. Test antibody (coupled to color-generating enzyme)—to see if a certain antigen is present

If the target substance is present in the sample, the test solution will have an intense color reaction, indicating a positive test result.

ELISA is used in many laboratories to determine whether a particular antibody (e.g., anti-HIV) is present in a patient's blood sample. Both the sensitivity and the specificity of ELISA approach 100%, but both false positive and false negative results do occur.

► BIOCHEMISTRY—GENETICS

Genetic terms

Variable expression	Nature and severity of the phenotype varies from 1 individual to another.
Incomplete penetrance	Not all individuals with a mutant genotype show the mutant phenotype.
Pleiotropy	1 gene has > 1 effect on an individual's phenotype.
Imprinting	Differences in phenotype depend on whether the mutation is of maternal or paternal origin (e.g., AngelMan's syndrome [Maternal], Prader-Willi syndrome [Paternal]).
Anticipation	Severity of disease worsens or age of onset of disease is earlier in succeeding generations (e.g., Huntington's disease).
Loss of heterozygosity	If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.
Dominant negative mutation	Exerts a dominant effect . A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.
Linkage disequilibrium	Tendency for certain alleles at 2 linked loci to occur together more often than expected by chance. Measured in a population, not in a family, and often varies in different populations.
Mosaicism	Occurs when cells in the body have different genetic makeup (e.g., lyonization—random X inactivation in females).
Locus heterogeneity	Mutations at different loci can produce the same phenotype (e.g., albinism).

Hardy-Weinberg population genetics

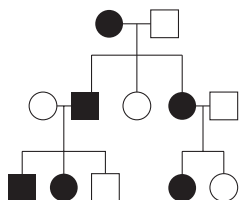
If a population is in Hardy-Weinberg equilibrium, then:
 Disease prevalence: $p^2 + 2pq + q^2 = 1$
 Allele prevalence: $p + q = 1$
 p and q are separate alleles; $2pq$ = heterozygote prevalence.

Hardy-Weinberg law assumes:

1. There is no mutation occurring at the locus
2. There is no selection for any of the genotypes at the locus
3. Mating is completely random
4. There is no migration into or out of the population being considered

Modes of inheritance

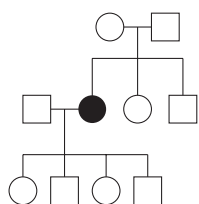
Autosomal dominant



Often due to defects in structural genes. Many generations, both male and female, affected.

Often pleiotropic and, in many cases, present clinically after puberty. Family history crucial to diagnosis.

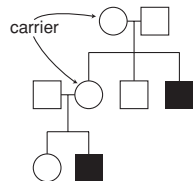
Autosomal recessive



25% of offspring from 2 carrier parents are affected. Often due to enzyme deficiencies. Usually seen in only 1 generation.

Commonly more severe than dominant disorders; patients often present in childhood.

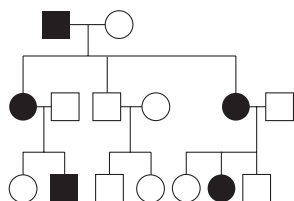
X-linked recessive



Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission.

Commonly more severe in males. Heterozygous females may be affected.

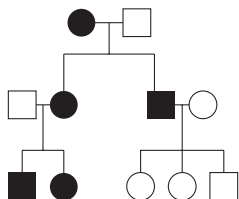
X-linked dominant



Transmitted through both parents. Either male or female offspring of the affected mother may be affected, while **all** female offspring of the affected father are diseased.

Hypophosphatemic rickets.

Mitochondrial inheritance



Transmitted only through mother. All offspring of affected females may show signs of disease.

Leber's hereditary optic neuropathy; mitochondrial myopathies.

► BIOCHEMISTRY—GENETICS (*continued*)**Autosomal-dominant diseases**

Adult polycystic kidney disease	Always bilateral , massive enlargement of kidneys due to multiple large cysts. Patients present with pain, hematuria, hypertension, progressive renal failure. 90% of cases are due to mutation in <i>APKD1</i> (chromosome 16). Associated with polycystic liver disease, berry aneurysms , mitral valve prolapse. Juvenile form is recessive.
Familial hypercholesterolemia (hyperlipidemia type IIA)	Elevated LDL owing to defective or absent LDL receptor. Heterozygotes (1:500) have cholesterol \approx 300 mg/dL. Homozygotes (very rare) have cholesterol \approx 700+ mg/dL, severe atherosclerotic disease early in life, and tendon xanthomas (classically in the Achilles tendon); MI may develop before age 20.
Marfan's syndrome	Fibrillin gene mutation \rightarrow connective tissue disorders. Skeletal abnormalities—tall with long extremities (arachnodactyly), hyperextensive joints, and long, tapering fingers and toes (see Image 109). Cardiovascular—cystic medial necrosis of aorta \rightarrow aortic incompetence and dissecting aortic aneurysms. Floppy mitral valve. Ocular—subluxation of lenses.
Neurofibromatosis type 1 (von Recklinghausen's disease)	Findings: café-au-lait spots, neural tumors, Lisch nodules (pigmented iris hamartomas). Also marked by skeletal disorders (e.g., scoliosis), pheochromocytoma, and \uparrow tumor susceptibility. On long arm of chromosome 17; 17 letters in von Recklinghausen.
Neurofibromatosis type 2	Bilateral acoustic neuroma, optic pathway gliomas, juvenile cataracts. <i>NF2</i> gene on chromosome 22; type 2 = 22.
Tuberous sclerosis	Findings: facial lesions (adenoma sebaceum), hypopigmented “ash leaf spots” on skin, cortical and retinal hamartomas, seizures, mental retardation, renal cysts, cardiac rhabdomyomas. Incomplete penetrance, variable presentation.
Von Hippel–Lindau disease	Findings: hemangioblastomas of retina/cerebellum/medulla; about half of affected individuals develop multiple bilateral renal cell carcinomas and other tumors. Associated with deletion of <i>VHL</i> gene (tumor suppressor) on chromosome 3 (3p). Von Hippel–Lindau = 3 words for chromosome 3.
Huntington's disease	Findings: depression, progressive dementia, choreiform movements, caudate atrophy, and \downarrow levels of GABA and ACh in the brain. Symptoms manifest in affected individuals between the ages of 20 and 50. Gene located on chromosome 4; triplet repeat disorder. “Hunting 4 food.”
Familial adenomatous polyposis	Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless resected. Deletion on chromosome 5; 5 letters in “polyp.”
Hereditary spherocytosis	Spheroid erythrocytes; hemolytic anemia; increased MCHC. Splenectomy is curative.
Achondroplasia	Autosomal-dominant cell-signaling defect of fibroblast growth factor (FGF) receptor 3. Results in dwarfism; short limbs, but head and trunk are normal size.

Autosomal-recessive diseases

Cystic fibrosis, albinism, α_1 -antitrypsin deficiency, phenylketonuria, thalassemias, sickle cell anemias, glycogen storage diseases, mucopolysaccharidoses (except Hunter's), sphingolipidoses (except Fabry's), infant polycystic kidney disease, hemochromatosis.

Cystic fibrosis	Autosomal-recessive defect in <i>CFTR</i> gene on chromosome 7. Defective Cl^- channel \rightarrow secretion of abnormally thick mucus that plugs lungs, pancreas, and liver \rightarrow recurrent pulmonary infections (<i>Pseudomonas</i> species and <i>S. aureus</i>), chronic bronchitis, bronchiectasis, pancreatic insufficiency (malabsorption and steatorrhea), meconium ileus in newborns. \uparrow concentration of Cl^- ions in sweat test is diagnostic.	Infertility in males due to absent vas deferens. Fat-soluble vitamin deficiencies (A, D, E, K). Can present as failure to thrive in infancy. Most common lethal genetic disease of Caucasians. Treatment: N-acetylcysteine to loosen mucous plugs.
X-linked recessive disorders	Fragile X, Duchenne's muscular dystrophy, hemophilia A and B, Fabry's, G6PD deficiency, Hunter's syndrome, ocular albinism, Lesch-Nyhan syndrome, Bruton's agammaglobulinemia, Wiskott-Aldrich syndrome. Female carriers of X-linked recessive disorders are rarely affected because of random inactivation of X chromosomes in each cell.	
Muscular dystrophies		
Duchenne's (X-linked)	Frame-shift mutation \rightarrow deletion of dystrophin gene \rightarrow accelerated muscle breakdown. Onset before 5 years of age. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle; cardiac myopathy. The use of Gowers' maneuver, requiring assistance of the upper extremities to stand up, is characteristic (indicates proximal lower limb weakness).	Duchenne's = Deleted Dystrophin. Diagnose muscular dystrophies by \uparrow CPK and muscle biopsy.
Becker's	Mutated dystrophin gene is less severe than Duchenne's.	
Fragile X syndrome	X-linked defect affecting the methylation and expression of the <i>FMRI</i> gene. The 2nd most common cause of genetic mental retardation (the most common cause is Down syndrome). Associated with macro-orchidism (enlarged testes), long face with a large jaw, large everted ears, and autism.	Triplet repeat disorder (CGG) _n that may show genetic anticipation (germlike expansion in females). Fragile X = eXtra-large testes, jaw, ears.
Trinucleotide repeat expansion diseases	Huntington's disease, myotonic dystrophy, Friedreich's ataxia, fragile X syndrome. May show anticipation (disease severity \uparrow and age of onset \downarrow in successive generations).	Try (trinucleotide) hunting for my fried eggs (X).
Common congenital malformations	1. Heart defects 2. Hypospadias 3. Cleft lip (with or without cleft palate) 4. Congenital hip dislocation 5. Spina bifida 6. Anencephaly 7. Pyloric stenosis	Associated with projectile vomiting.

► BIOCHEMISTRY–GENETICS (*continued*)**Autosomal trisomies**

Down syndrome
(trisomy 21), 1:700

Most common chromosomal disorder and cause of congenital mental retardation. Findings: mental retardation, flat facial profile, prominent epicanthal folds, simian crease, duodenal atresia, congenital heart disease (most common malformation is septum primum–type ASD due to endocardial cushion defects), Alzheimer's disease in affected individuals > 35 years old, ↑ risk of ALL.

Drinking age (21).
↓ levels of α -fetoprotein,
↑ β -hCG, ↑ nuchal
translucency.

95% of cases due to meiotic nondisjunction of homologous chromosomes; associated with advanced maternal age (from 1:1500 in women < 20 to 1:25 in women > 45). 4% of cases due to Robertsonian translocation, and 1% of cases due to Down mosaicism (no maternal association) (see Image 110).

Edwards' syndrome
(trisomy 18),
1:8000

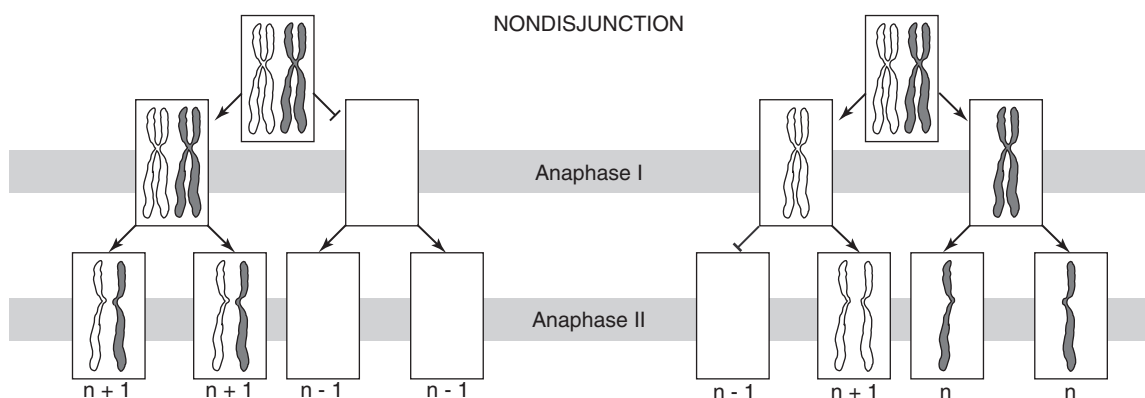
Findings: severe mental retardation, rocker bottom feet, low-set ears, micrognathia (small jaw), congenital heart disease, clenched hands, prominent occiput. Death usually occurs within 1 year of birth.

Election age (18).

Patau's syndrome
(trisomy 13),
1:6000

Findings: severe mental retardation, microphthalmia, microcephaly, cleft lip/palate, abnormal forebrain structures, polydactyly, congenital heart disease. Death usually occurs within 1 year of birth.

Puberty (13).

**Cri-du-chat syndrome**

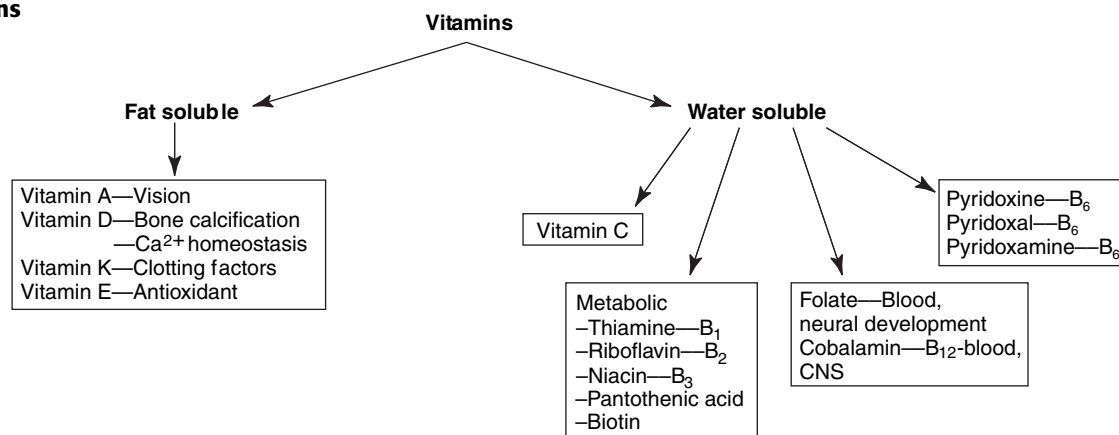
Congenital deletion of short arm of chromosome 5 (46,XX or XY, 5p-).
Findings: microcephaly, severe mental retardation, high-pitched crying/mewing, epicanthal folds, cardiac abnormalities.

Cri du chat = cry of the cat.

22q11 syndromes	Cleft palate, Abnormal facies, Thymic aplasia → T-cell deficiency, Cardiac defects, Hypocalcemia 2° to parathyroid aplasia, microdeletion at chromosome 22q11. Variable presentation as DiGeorge syndrome (thymic, parathyroid, and cardiac defects) or velocardiofacial syndrome (palate, facial, and cardiac defects).	CATCH-22.
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Fetal alcohol syndrome	Newborns of mothers who consumed significant amounts of alcohol (teratogen) during pregnancy (highest risk at 3–8 weeks) have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities, limb dislocation, and heart and lung fistulas. Mechanism may include inhibition of cell migration. The number one cause of congenital malformations in the United States.	
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► BIOCHEMISTRY—NUTRITION

Vitamins**Vitamins: fat soluble**

A, D, E, K. Absorption dependent on gut (ileum) and pancreas. Toxicity more common than for water-soluble vitamins, because these accumulate in fat.

Malabsorption syndromes (steatorrhea), such as cystic fibrosis and sprue, or mineral oil intake can cause fat-soluble vitamin deficiencies.

Vitamins: water soluble

B₁ (thiamine: TPP)
B₂ (riboflavin: FAD, FMN)
B₃ (niacin: NAD⁺)
B₅ (pantothenate: CoA)
B₆ (pyridoxine: PP)
B₁₂ (cobalamin)
C (ascorbic acid)
Biotin
Folate

All wash out easily from body except B₁₂ (stored in liver). B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.

Vitamin A (retinol)

Deficiency Night blindness, dry skin, and impaired immune response.
Function Constituent of visual pigments (retinal).
Excess Arthralgias, fatigue, headaches, skin changes, sore throat, alopecia.

Retinol is vitamin **A**, so think **Retin-A** (used topically for wrinkles and acne).

Vitamin B₁ (thiamine)

Deficiency Beriberi and Wernicke-Korsakoff syndrome. Seen in alcoholism and malnutrition.
Function In thiamine pyrophosphate, a cofactor for oxidative decarboxylation of α -keto acids (pyruvate, α -ketoglutarate) and a cofactor for transketolase in the HMP shunt.

Spell beriberi as **Ber1Ber1**.
Dry beriberi—polyneuritis, muscle wasting.
Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

Vitamin B₂ (riboflavin)

Deficiency	Angular stomatitis, Cheilosis, Corneal vascularization.	The 2 C's. FAD and FMN are derived from riboFlavin (B ₂ = 2 ATP).
Function	Cofactor in oxidation and reduction (e.g., FADH ₂).	

Vitamin B₃ (niacin)

Deficiency	Pellagra can be caused by Hartnup disease (↓ tryptophan absorption), malignant carcinoid syndrome (↑ tryptophan metabolism), and INH (↓ vitamin B ₆).	Pellagra's symptoms are the 3 D's: Diarrhea, Dermatitis, Dementia (also beefy glossitis).
Function	Constituent of NAD ⁺ , NADP ⁺ (used in redox reactions). Derived from tryptophan using vitamin B ₆ .	NAD derived from Niacin (B ₃ = 3 ATP).

Vitamin B₅ (pantothenate)

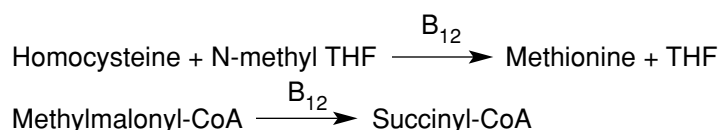
Deficiency	Dermatitis, enteritis, alopecia, adrenal insufficiency.	
Function	Constituent of CoA (a cofactor for acyl transfers) and component of fatty acid synthase.	Pantothen-A is in Co-A.

Vitamin B₆ (pyridoxine)

Deficiency	Convulsions, hyperirritability (deficiency inducible by INH and oral contraceptives), peripheral neuropathy.	
Function	Converted to pyridoxal phosphate, a cofactor used in transamination (e.g., ALT and AST), decarboxylation, and heme synthesis.	

Vitamin B₁₂ (cobalamin)

Deficiency	Macrocytic, megaloblastic anemia; neurologic symptoms (optic neuropathy, subacute combined degeneration, paresthesia); glossitis.	Found only in animal products. Vitamin B ₁₂ deficiency is usually caused by malabsorption (sprue, enteritis, <i>Diphyllobothrium latum</i>), lack of intrinsic factor (pernicious anemia), or absence of terminal ileum (Crohn's disease).
Function	Cofactor for homocysteine methylation (transfers CH ₃ groups as methylcobalamin) and methylmalonyl-CoA handling. Stored primarily in the liver. Synthesized only by microorganisms.	Use Schilling test to detect deficiency. Abnormal myelin is seen in B ₁₂ deficiency, possibly due to ↓ methionine or ↑ methylmalonic acid (from metabolism of accumulated methylmalonyl-CoA).



► BIOCHEMISTRY–NUTRITION (*continued*)**Folic acid**

Deficiency	Most common vitamin deficiency in the United States. Macrocytic, megaloblastic anemia (often no neurologic symptoms, as opposed to vitamin B ₁₂ deficiency).	FOL ate from FOL iage. Eat green leaves (because folic acid is not stored very long). Supplemental folic acid in early pregnancy reduces neural tube defects.
Function	Coenzyme (tetrahydrofolate) for 1-carbon transfer; involved in methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.	PABA is the folic acid precursor in bacteria. Sulfonamides and dapsone (antimicrobials) are PABA analogs.

Biotin

Deficiency	Dermatitis, enteritis. Caused by antibiotic use, ingestion of raw eggs.	“ AVID in in egg whites AVID ly binds biotin.”
Function	Cofactor for carboxylations: 1. Pyruvate → oxaloacetate 2. Acetyl-CoA → malonyl-CoA 3. Propionyl-CoA → methylmalonyl-CoA	

Vitamin C (ascorbic acid)

Deficiency	Scurvy—swollen gums, bruising, anemia, poor wound healing.	Vitamin C Cross-links
Function	Necessary for hydroxylation of proline and lysine in collagen synthesis. Facilitates iron absorption by keeping iron in Fe ²⁺ reduced state (more absorbable) Necessary as a cofactor for dopamine → NE.	Collagen. British sailors carried limes to prevent scurvy (origin of the word “limey”).

Vitamin D

	D ₂ = ergocalciferol, consumed in milk. D ₃ = cholecalciferol, formed in sun-exposed skin. 25-OH D ₃ = storage form. 1,25 (OH) ₂ D ₃ = active form.	Remember that drinking milk (fortified with vitamin D) is good for bones.
Deficiency	Rickets in children (bending bones), osteomalacia in adults (soft bones), and hypocalcemic tetany.	
Function	↑ intestinal absorption of calcium and phosphate.	
Excess	Hypercalcemia, loss of appetite, stupor. Seen in sarcoidosis, a disease where the epithelioid macrophages convert vitamin D into its active form.	

Vitamin E

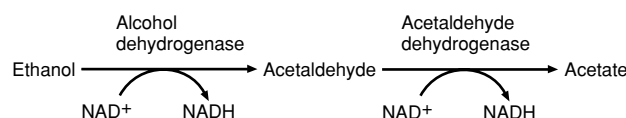
Deficiency	Increased fragility of erythrocytes.	Vitamin E is for Erythrocytes.
Function	Antioxidant (protects erythrocytes from hemolysis).	

Vitamin K

Deficiency

Neonatal hemorrhage with \uparrow PT and \uparrow aPTT but normal bleeding time.

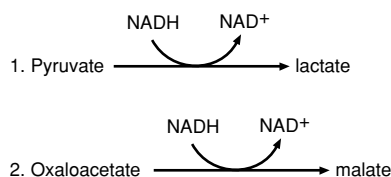
Function

Catalyzes γ -carboxylation of glutamic acid residues on various proteins concerned with blood clotting. Synthesized by intestinal flora. Therefore, vitamin K deficiency can occur after the prolonged use of broad-spectrum antibiotics.**K** for **K**oagulation. Note that the vitamin K–dependent clotting factors are II, VII, IX, X, and protein C and S. Warfarin is a vitamin K antagonist.**Zinc deficiency**Delayed wound healing, hypogonadism, \downarrow adult hair (axillary, facial, pubic); may predispose to alcoholic cirrhosis.**Ethanol metabolism**

Disulfiram (Antabuse) inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms).

NAD⁺ is the limiting reagent.

Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol hypoglycemiaEthanol metabolism \uparrow NADH/NAD⁺ ratio in liver, causing diversion of pyruvate to lactate and OAA to malate, thereby inhibiting gluconeogenesis and leading to hypoglycemia. This altered NADH/NAD⁺ ratio is responsible for the hepatic fatty change (hepatocellular steatosis) seen in chronic alcoholics (shunting away from glycolysis and toward fatty acid synthesis).**Kwashiorkor vs. marasmus**

Kwashiorkor—protein malnutrition resulting in skin lesions, edema, liver malfunction (fatty change). Clinical picture is small child with swollen belly.

Marasmus—protein-calorie malnutrition resulting in tissue wasting.

Kwashiorkor results from a protein-deficient **MEAL**:

- M**alabsorption
- E**dema
- A**nemia
- L**iver (fatty)

[illegible]

Embryology

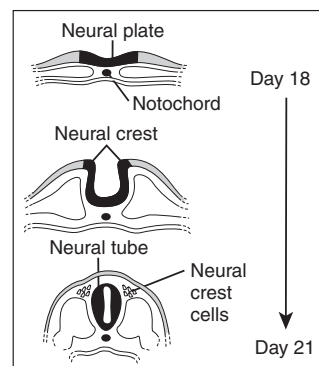
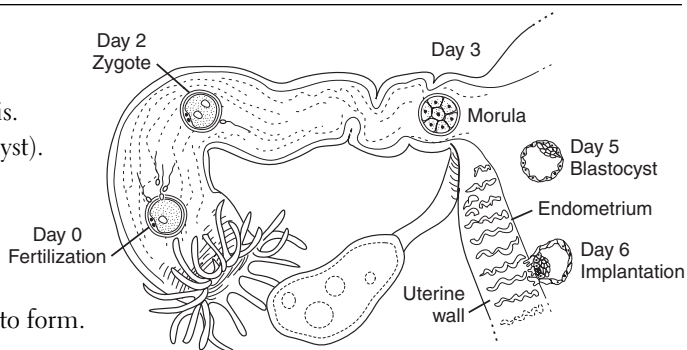
“Zygote. This cell, formed by the union of an ovum and a sperm, represents the beginning of a human being.”

—Keith Moore and Vid Persaud,
Before We Are Born

Embryology is traditionally one of the higher-yield areas within anatomy. This topic can be crammed closer to the exam date. Many questions focus on underlying mechanisms of congenital malformations (e.g., failure of fusion of the maxillary and medial nasal processes leading to cleft palate).

Fetal landmarks

Day 0	Fertilization by sperm, initiating embryogenesis.
Within week 1	Implantation (as a blastocyst).
Within week 2	Bilaminar disk.
Within week 3	Gastrulation. Primitive streak, notochord, and neural plate begin to form.
Weeks 3–8	Neural tube formed. Organogenesis. Extremely susceptible to teratogens.
Week 4	Heart begins to beat.
Week 10	Upper and lower limb buds begin to form. Genitalia have male/female characteristics.

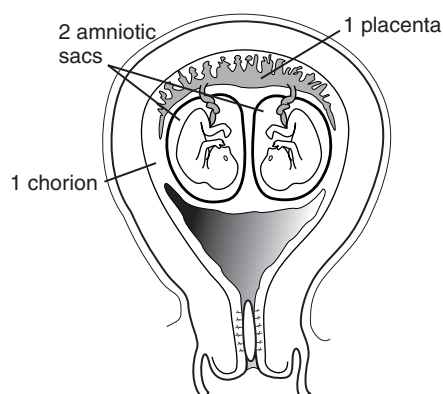
**Early development**

Rule of 2's for 2nd week	2 germ layers (bilaminar disk): epiblast, hypoblast. 2 cavities: amniotic cavity, yolk sac. 2 components to placenta: cytotrophoblast, syncytiotrophoblast.	The epiblast (precursor to ectoderm) invaginates to form primitive streak. Cells from the primitive streak give rise to both intraembryonic mesoderm and endoderm.
Rule of 3's for 3rd week	3 germ layers (gastrula): ectoderm, mesoderm, endoderm.	

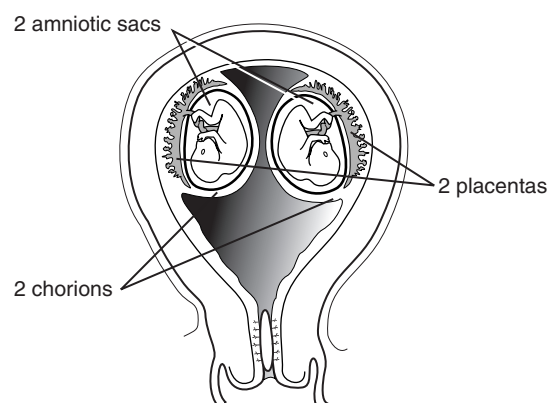
Embryologic derivatives

Ectoderm	
Surface ectoderm	Adenohypophysis, lens of eye, epithelial linings, epidermis.
Neuroectoderm	Neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland.
Neural crest	ANS, dorsal root ganglia, cranial nerves, melanocytes, chromaffin cells of adrenal medulla, enterochromaffin cells, pia and arachnoid, celiac ganglion, Schwann cells, odontoblasts, parafollicular (C) cells of thyroid, laryngeal cartilage, bones of the skull.
Mesoderm	Dura mater, connective tissue, muscle, bone, cardiovascular structures, lymphatics, blood, urogenital structures, serous linings of body cavities (e.g., peritoneal), spleen, adrenal cortex, kidneys.
Endoderm	Gut tube epithelium and derivatives (e.g., lungs, liver, pancreas, thymus, parathyroid, thyroid follicular cells).
Notochord	Induces ectoderm to form neuroectoderm (neural plate). Its postnatal derivative is the nucleus pulposus of the intervertebral disk.

Teratogens	Most susceptible in 3rd–8th weeks (organogenesis) of pregnancy.	
Examples		Effects on fetus
Alcohol		Birth defects and mental retardation (leading cause); fetal alcohol syndrome
ACE inhibitors		Renal damage
Cocaine		Abnormal fetal development and fetal addiction
Diethylstilbestrol (DES)		Vaginal clear cell adenocarcinoma
Iodide		Congenital goiter or hypothyroidism
13- <i>cis</i> -retinoic acid		Extremely high risk for birth defects
Thalidomide		Limb defects (“flipper” limbs)
Tobacco		Preterm labor, placental problems, attention-deficit hyperactivity disorder (ADHD)
Warfarin, x-rays		Multiple anomalies
Fetal infections can also cause congenital malformations. (Other medications contraindicated in pregnancy are shown in the pharmacology section.)		

Twinning**Monozygotic**

1 zygote splits evenly to develop 2 amniotic sacs with a single common chorion and placenta.

Dizygotic (fraternal) or monozygotic

Dizygotes develop individual placentas, chorions, and amniotic sacs.

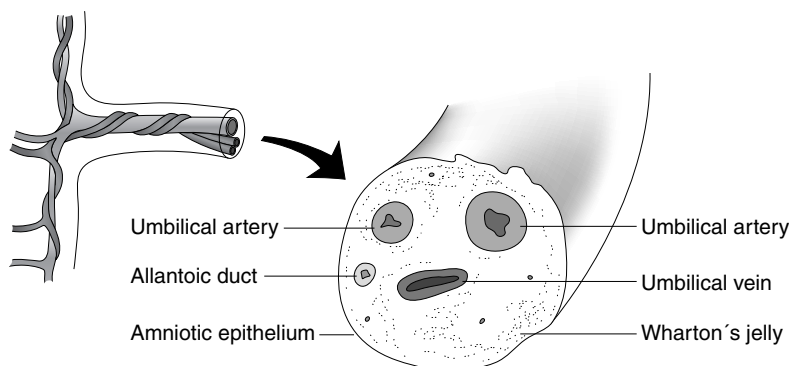
Monozygotes develop 2 placentas (separate/fused), chorions, and amniotic sacs.

Umbilical cord

Contains 2 umbilical arteries, which return deoxygenated blood from fetal internal iliac arteries, and 1 umbilical vein, which supplies oxygenated blood from the placenta to the fetus.

Allantoic duct removes nitrogenous waste (from fetal bladder, like a urethra).

Single umbilical artery is associated with congenital and chromosomal anomalies.

**Heart embryology****Embryonic structure**

Truncus arteriosus

Bulbus cordis

Primitive ventricle

Primitive atria

Left horn of sinus venosus (SV)

Right horn of SV

Right common cardinal vein and right anterior cardinal vein

Gives rise to

Ascending aorta and pulmonary trunk

Smooth parts of left and right ventricle

Trabeculated parts of left and right ventricle

Trabeculated left and right atrium

Coronary sinus

Smooth part of right atrium

SVC

Fetal erythropoiesis

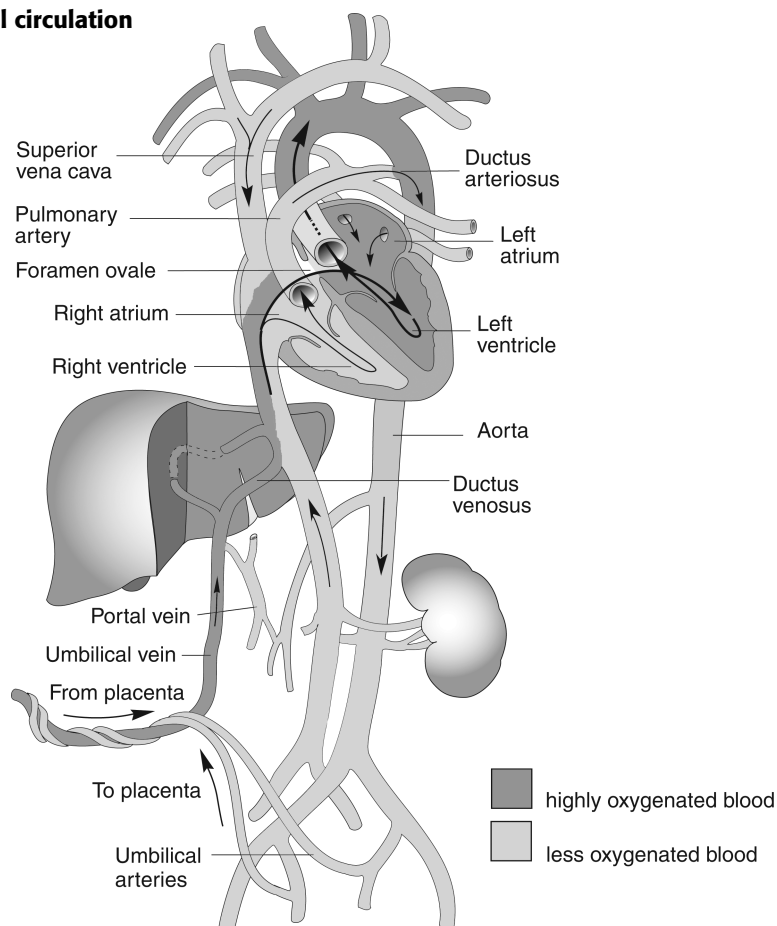
Fetal erythropoiesis occurs in:

1. Yolk sac (3–8 wk)
2. Liver (6–30 wk)
3. Spleen (9–28 wk)
4. Bone marrow (28 wk onward)

Young Liver Synthesizes Blood.

Fetal hemoglobin = $\alpha_2\gamma_2$.

Adult hemoglobin = $\alpha_2\beta_2$.

Fetal circulation

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 19th ed. Stamford, CT: Appleton & Lange, 1999:600.)

Blood in umbilical vein is $\approx 80\%$ saturated with O_2 .

3 important shunts:

1. Most oxygenated blood reaching the heart via the IVC is diverted through the **foramen ovale** and pumped out the aorta to the head.
2. Deoxygenated blood from the SVC is expelled into the pulmonary artery and **ductus arteriosus** to the lower body of the fetus.
3. Blood entering the fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC.

At birth, infant takes a breath;
 \downarrow resistance in pulmonary vasculature causes \uparrow left atrial pressure vs. right atrial pressure; foramen ovale closes; \uparrow in O_2 leads to \downarrow in prostaglandins, causing closure of ductus arteriosus.

Indomethacin closes the PDA.

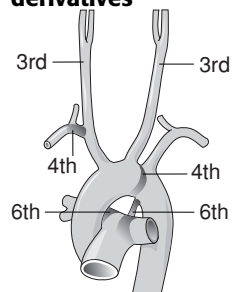
Prostaglandins keep a patent PDA open.

Fetal-postnatal derivatives

1. Umbilical vein—ligamentum teres hepatis
2. Umbilical arteries—**media**L umbilical ligaments
3. Ductus arteriosus—ligamentum arteriosum
4. Ductus venosus—ligamentum venosum
5. Foramen ovale—fossa ovalis
6. **Alla**Ntois—urachus—**media**N umbilical ligament
7. Notochord—nucleus pulposus of intervertebral disk

The urachus is the part of the allantoic duct between the bladder and the umbilicus.

Urachal cyst or sinus is a remnant.

Aortic arch derivatives

- 1st—part of **MAX**illary artery.
- 2nd—**Stapedial** artery and hyoid artery.
- 3rd—common **Carotid** artery and proximal part of internal carotid artery.
- 4th—on left, aortic arch; on right, proximal part of right subclavian artery.
- 6th—proximal part of pulmonary arteries and (on left only) ductus arteriosus.

1st arch is **MAX**imal.

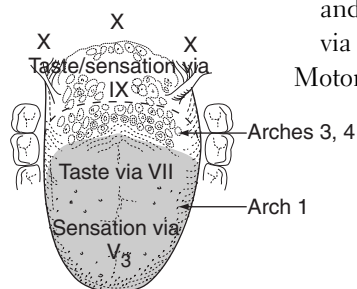
Second = **Stapedial**.

C is 3rd letter of alphabet.

4th arch (4 limbs) = systemic.

6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).

Branchial apparatus	Composed of branchial clefts, arches, and pouches. Branchial clefts are derived from ectoderm. Branchial arches are derived from mesoderm and neural crests. Branchial pouches are derived from endoderm.	CAP covers outside from inside (Clefts = ectoderm, Arches = mesoderm, Pouches = endoderm). Branchial apparatus is also called pharyngeal apparatus. Clefts are also called grooves.
Branchial arch 1 derivatives	Meckel's cartilage: Mandible, Malleus, incus, sphenomandibular ligament. Muscles: Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini, anterior ⅔ of tongue. Nerve: CN V ₂ and CN V ₃ .	
Branchial arch 2 derivatives	Reichert's cartilage: Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament. Muscles: muscles of facial expression, Stapedius, Stylohyoid, posterior belly of digastric. Nerve: CN VII.	
Branchial arch 3 derivatives	Cartilage: greater horn of hyoid. Muscle: stylopharyngeus. Nerve: CN IX.	Think of pharynx: stylo pharyngeus innervated by gloss pharyngeal nerve.
Branchial arches 4–6 derivatives	Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform. Muscles (4th arch): most pharyngeal constrictors, cricothyroid, levator veli palatini. Muscles (6th arch): all intrinsic muscles of larynx except cricothyroid . Nerve: 4th arch—CN X (superior laryngeal branch); 6th arch—CN X (recurrent laryngeal branch).	Arches 3 and 4 form posterior ⅓ of tongue. Arch 5 makes no major developmental contributions.
Branchial arch innervation	Arch 1 derivatives supplied by CN V ₂ and V ₃ . Arch 2 derivatives supplied by CN VII. Arch 3 derivatives supplied by CN IX. Arch 4 and 6 derivatives supplied by CN X.	

Tongue development

1st branchial arch forms anterior $\frac{2}{3}$ (thus sensation via CN V₃, taste via CN VII).

3rd and 4th arches form posterior $\frac{1}{3}$ (thus sensation and taste mainly via CN IX, extreme posterior via CN X).

Motor innervation is via CN XII.

Taste is CN VII, IX, X (solitary nucleus); pain is CN V₃, IX, X; motor is CN XII.

Branchial cleft derivatives

1st cleft develops into external auditory meatus.
2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

Persistent cervical sinus can lead to a branchial cyst in the neck.

Ear development**Bones**

Malleus/incus—1st arch

Stapes—2nd arch

Muscles

Tensor tympani (V₃)—1st arch

Stapedius (VII)—2nd arch

Miscellaneous

External auditory meatus—1st cleft

Eardrum, eustachian tube—1st branchial membrane (branchial membranes are located at junctions of clefts with pouches)

Branchial pouch derivatives

1st pouch develops into middle ear cavity, eustachian tube, mastoid air cells.

2nd pouch develops into epithelial lining of palatine tonsil.

3rd pouch (dorsal wings) develops into **inferior** parathyroids.

3rd pouch (ventral wings) develops into thymus.

4th pouch develops into **superior** parathyroids.

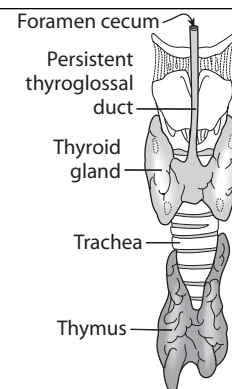
1st pouch contributes to endoderm-lined structures of ear.

3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids).

Aberrant development of 3rd and 4th pouches → DiGeorge syndrome → leads to T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development).

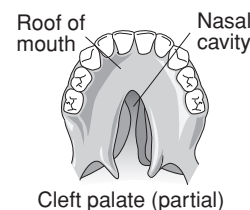
Thyroid development

Thyroid diverticulum arises from floor of primitive pharynx, descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue.

**Cleft lip and cleft palate**

Cleft lip

Cleft lip—failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).
Cleft palate—failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine process (formation of 2° palate).

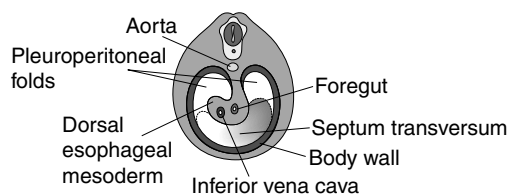


Cleft palate (partial)

Diaphragm embryology

Diaphragm is derived from:

1. Septum transversum
2. Pleuroperitoneal folds
3. Body wall
4. Dorsal mesentery of esophagus

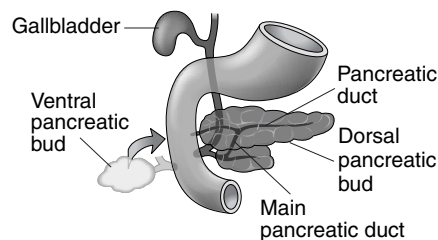
**Several Parts Build Diaphragm.**

Diaphragm descends during development but maintains innervation from above C3–C5. “C3, 4, 5 keeps the diaphragm alive.”

Abdominal contents may herniate into the thorax due to incomplete development (hiatal hernia).

Pancreas and spleen embryology

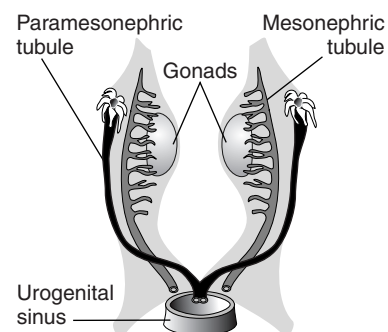
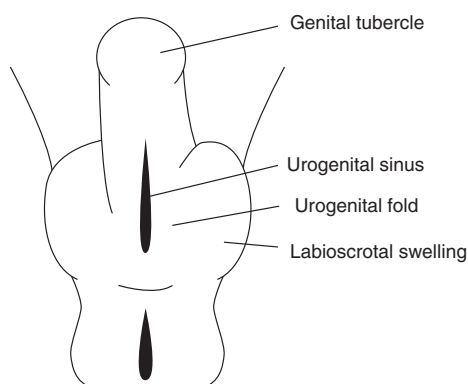
Pancreas is derived from the foregut. Ventral pancreatic bud becomes pancreatic head, uncinate process (lower half of head), and main pancreatic duct. Dorsal pancreatic bud becomes everything else (body, tail, isthmus, and accessory pancreatic duct).
Spleen arises from dorsal mesentery but is supplied by artery of foregut.
Annular pancreas—ventral and dorsal pancreatic buds abnormally encircle duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing.



Genital ducts

Mesonephric
(wolffian) duct
Paramesonephric
(müllerian) duct

Develops into Seminal vesicles, Epididymis,
Ejaculatory duct, and Ductus deferens.
Develops into fallopian tube, uterus, and part of
vagina.
Müllerian inhibiting substance secreted
by testes suppresses development of
paramesonephric ducts in males.
↑ androgens cause development of mesonephric
ducts.

SEED.**Male/female genital homologues****Male**

Glans penis
Corpus spongiosum
Bulbourethral glands
(of Cowper)
Prostate gland
Ventral shaft of penis
(penile urethra)
Scrotum

Dihydrotestosterone
Genital tubercle
Urogenital sinus
Urogenital sinus
Urogenital sinus
Urogenital folds
Labioscrotal swelling

Female

Glans clitoris
Vestibular bulbs
Greater vestibular glands
(of Bartholin)
Urethral and paraurethral glands
(of Skene)
Labia minora
Labia majora

NOTES

Microbiology and Immunology

*“What lies behind us and what lies ahead of us are tiny matters
compared to what lives within us.”*

—Oliver Wendell Holmes

This high-yield material covers the basic concepts of microbiology and immunology. The emphasis in previous examinations has been approximately 40% bacteriology (20% basic, 20% quasi-clinical), 25% immunology, 25% virology (10% basic, 15% quasi-clinical), 5% parasitology, and 5% mycology. Learning the distinguishing characteristics, target organs, and method of spread of—as well as relevant laboratory tests for—major pathogens can improve your score substantially.

Many students preparing for this part of the boards make the mistake of studying bacteriology thoroughly without devoting sufficient time to the other topics. For this reason, learning immunology and virology thoroughly is high yield. Learn the components and mechanistic details of the immune response, including T cells, B cells, and the structure and function of immunoglobulins. Also learn the major immunodeficiency diseases (e.g., AIDS, agammaglobulinemia, DiGeorge syndrome). Knowledge of viral structures and genomes remains important as well.

- ▶ High-Yield Clinical Vignettes
- ▶ Clinical Bacteriology
- ▶ Bacteriology
- ▶ Mycology
- ▶ Parasitology
- ▶ Virology
- ▶ Systems
- ▶ Antimicrobials
- ▶ Immunology

MICROBIOLOGY AND IMMUNOLOGY—HIGH-YIELD CLINICAL VIGNETTES

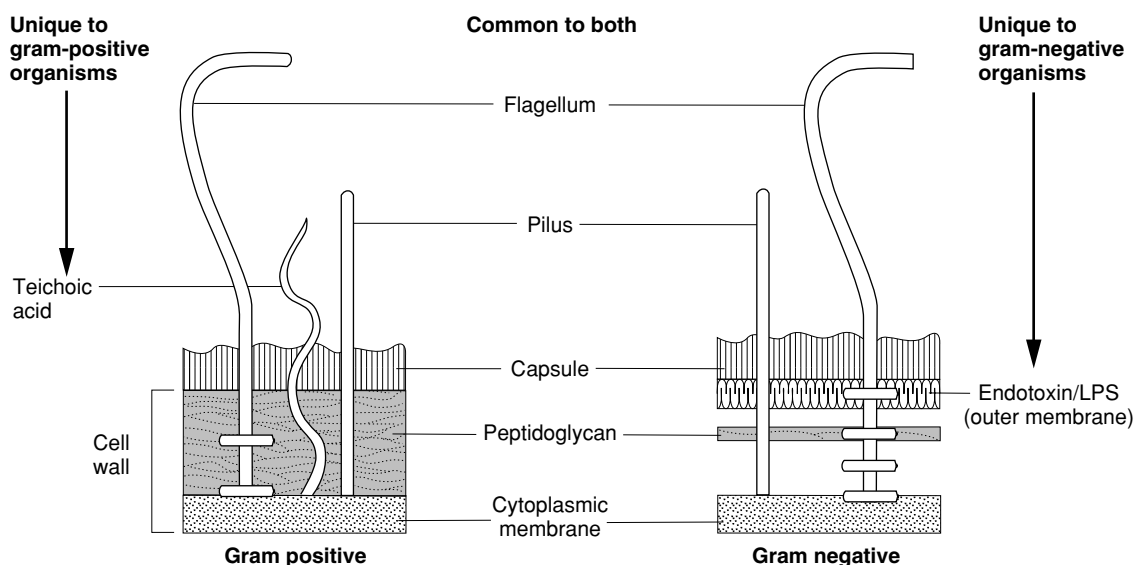
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| ■ Alcoholic vomits gastric contents and develops foul-smelling sputum. | What organisms are most likely? | Anaerobes. |
| ■ Middle-age male presents with acute-onset monoarticular joint pain and bilateral Bell's palsy. | What is the likely disease and how did he get it? | Lyme disease; bite from <i>Ixodes</i> tick. |
| ■ Patient with <i>Mycoplasma pneumoniae</i> exhibits cryoagglutinins during recovery phase. | What types of immunoglobulins are reacting? | IgM. |
| ■ UA of patient shows WBC casts. | What is the diagnosis? | Pyelonephritis. |
| ■ Young child presents with tetany and candidiasis. Hypocalcemia and immunosuppression are found. | What cell is deficient? | T cell (DiGeorge). |
| ■ Patient presents with "rose gardener's" scenario (thorn prick with ulcers along lymphatic drainage). | What is the infectious bug? | <i>Sporothrix schenckii</i> . |
| ■ 25-year-old medical student has a burning feeling in his gut after meals. Biopsy of gastric mucosa shows gram-negative rods. | What is the likely organism? | <i>H. pylori</i> . |
| ■ 32-year-old male has "cauliflower" skin lesions. Tissue biopsy shows broad-based budding yeasts. | What is the likely organism? | <i>Blastomyces</i> . |
| ■ Breast-feeding woman suddenly develops redness and swelling of her right breast. On examination, it is found to be a fluctuant mass. | What is the diagnosis? | Mastitis caused by <i>S. aureus</i> . |
| ■ Young child has recurrent lung infections and granulomatous lesions. | What is the defect in neutrophils? | NADPH oxidase (chronic granulomatous disease). |
| ■ 20-year-old college student presents with lymphadenopathy, fever, and hepatosplenomegaly. His serum agglutinates sheep RBCs. | What cell is infected? | B cell (EBV; infectious mononucleosis). |

- | | | |
|---|---|--|
| ■ One hour after eating custard at a picnic, a whole family began to vomit. After 10 hours, they were better. | What is the organism? | <i>S. aureus</i> (produces preformed enterotoxin). |
| ■ Infant becomes flaccid after eating honey. | What organism is implicated, and what is the mechanism of action? | <i>Clostridium botulinum</i> ; inhibited release of ACh. |
| ■ Man presents with squamous cell carcinoma of the penis. | He had exposure to what virus? | HPV. |
| ■ Patient develops endocarditis three weeks after receiving a prosthetic heart valve. | What organism is suspected? | <i>S. aureus</i> or <i>S. epidermidis</i> . |
| ■ 55-year-old man who is a smoker and a heavy drinker presents with a new cough and flulike symptoms. Gram stain shows no organisms; silver stain of sputum shows gram-negative rods. | What is the diagnosis? | <i>Legionella</i> pneumonia. |
| ■ After taking clindamycin, patient develops toxic megacolon and diarrhea. | What is the mechanism of diarrhea? | <i>Clostridium difficile</i> overgrowth. |

► MICROBIOLOGY AND IMMUNOLOGY—CLINICAL BACTERIOLOGY

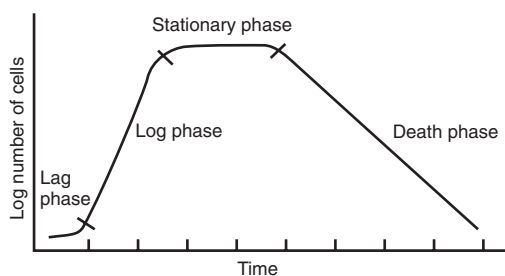
Bacterial structures

Structure	Function	Chemical composition
Peptidoglycan	Gives rigid support, protects against osmotic pressure.	Sugar backbone with cross-linked peptide side chains.
Cell wall/cell membrane (gram positives)	Major surface antigen.	Teichoic acid induces TNF and IL-1.
Outer membrane (gram negatives)	Site of endotoxin (lipopolysaccharide); major surface antigen.	Lipid A induces TNF and IL-1; polysaccharide is the antigen.
Plasma membrane	Site of oxidative and transport enzymes.	Lipoprotein bilayer.
Ribosome	Protein synthesis.	RNA and protein in 50S and 30S subunits.
Periplasm	Space between the cytoplasmic membrane and outer membrane in gram-negative bacteria.	Contains many hydrolytic enzymes, including β -lactamases.
Capsule	Protects against phagocytosis.	Polysaccharide (except <i>Bacillus anthracis</i> , which contains D-glutamate).
Pilus/fimbria	Mediates adherence of bacteria to cell surface; sex pilus forms attachment between 2 bacteria during conjugation.	Glycoprotein.
Flagellum	Motility.	Protein.
Spore	Provides resistance to dehydration, heat, and chemicals.	Keratin-like coat; dipicolinic acid.
Plasmid	Contains a variety of genes for antibiotic resistance, enzymes, and toxins.	DNA.
Glycocalyx	Mediates adherence to surfaces, especially foreign surfaces (e.g., indwelling catheters).	Polysaccharide.

Cell walls

(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:7.)

Bacterial growth curve



Lag—metabolic activity without division.

Log—rapid cell division.

Stationary—nutrient depletion slows growth.

Death—prolonged nutrient depletion and buildup of waste products lead to death.

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:15.)

Main features of exotoxins and endotoxins

Property	Exotoxin	Endotoxin
Source	Certain species of some gram-positive and gram-negative bacteria	Cell wall of most gram-negative bacteria and <i>Listeria</i>
Secreted from cell	Yes	No
Chemistry	Polypeptide	Lipopolysaccharide
Location of genes	Plasmid or bacteriophage	Bacterial chromosome
Toxicity	High (fatal dose on the order of 1 µg)	Low (fatal dose on the order of hundreds of micrograms)
Clinical effects	Various effects (see text)	Fever, shock
Mode of action	Various modes (see text)	Includes TNF and IL-1
Antigenicity	Induces high-titer antibodies called antitoxins	Poorly antigenic
Vaccines	Toxoids used as vaccines	No toxoids formed and no vaccine available
Heat stability	Destroyed rapidly at 60°C (except staphylococcal enterotoxin)	Stable at 100°C for 1 hour
Typical diseases	Tetanus, botulism, diphtheria	Meningococcemia, sepsis by gram-negative rods

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:39.)

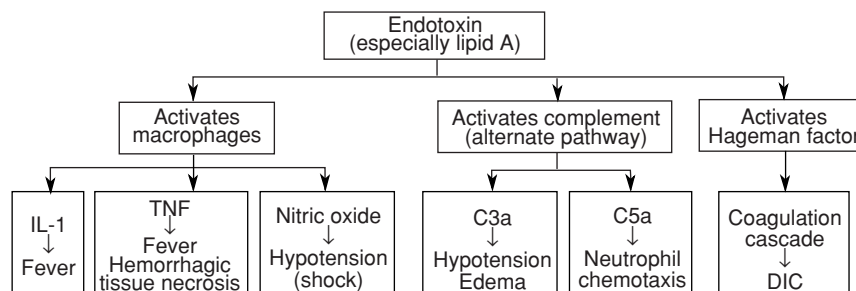
► MICROBIOLOGY AND IMMUNOLOGY—CLINICAL BACTERIOLOGY (*continued*)**Bugs with exotoxins**

Superantigens	Bind directly to MHC II and T-cell receptor, activating large numbers of T cells to stimulate release of IL-1 and IL-2.
<i>S. aureus</i>	TSST-1 causes toxic shock syndrome (fever, rash, shock). Enterotoxins cause food poisoning.
<i>S. pyogenes</i>	Scarlet fever—strain SPE toxin causes toxic shock–like syndrome.
ADP ribosylating A-B toxins	Interfere with host cell function. B (binding) component binds to a receptor on surface of host cell, enabling endocytosis. A (active) component then attaches an ADP-ribosyl to a host cell protein (ADP ribosylation), altering protein function.
<i>Corynebacterium diphtheriae</i>	Inactivates elongation factor (EF-2) (similar to <i>Pseudomonas</i> exotoxin A); causes pharyngitis and “pseudomembrane” in throat.
<i>Vibrio cholerae</i>	ADP ribosylation of G protein stimulates adenylyl cyclase; increases pumping of Cl [−] and H ₂ O into gut; causes voluminous rice-water diarrhea.
<i>E. coli</i>	Heat-labile toxin stimulates adenylyl cyclase (cholera-like mechanism), causing watery diarrhea. Heat-stable toxin stimulates guanylate cyclase.
<i>Bordetella pertussis</i>	Stimulates adenylyl cyclase; causes whooping cough; inhibits chemokine receptor, causing lymphocytosis.
Other toxins	
<i>Clostridium perfringens</i>	α toxin causes gas gangrene; get double zone of hemolysis on blood agar.
<i>C. tetani</i>	Blocks the release of inhibitory neurotransmitter glycine; causes “lockjaw.”
<i>C. botulinum</i>	Blocks the release of acetylcholine; causes anticholinergic symptoms, CNS paralysis; spores found in canned food, honey (causes floppy baby).
<i>Bacillus anthracis</i>	I toxin in the toxin complex is an adenylyl cyclase.
<i>Shigella</i>	Shiga toxin (also produced by <i>E. coli</i> O157:H7) cleaves host cell rRNA; also enhances cytokine release, causing HUS.
<i>S. pyogenes</i>	Streptolysin O is a hemolysin; antigen for ASO antibody in rheumatic fever.

Endotoxin

A lipopolysaccharide found in cell wall of gram-negative bacteria.

N-dotoxin is an integral part of gram-Negative cell wall.
Endotoxin is heat stable.

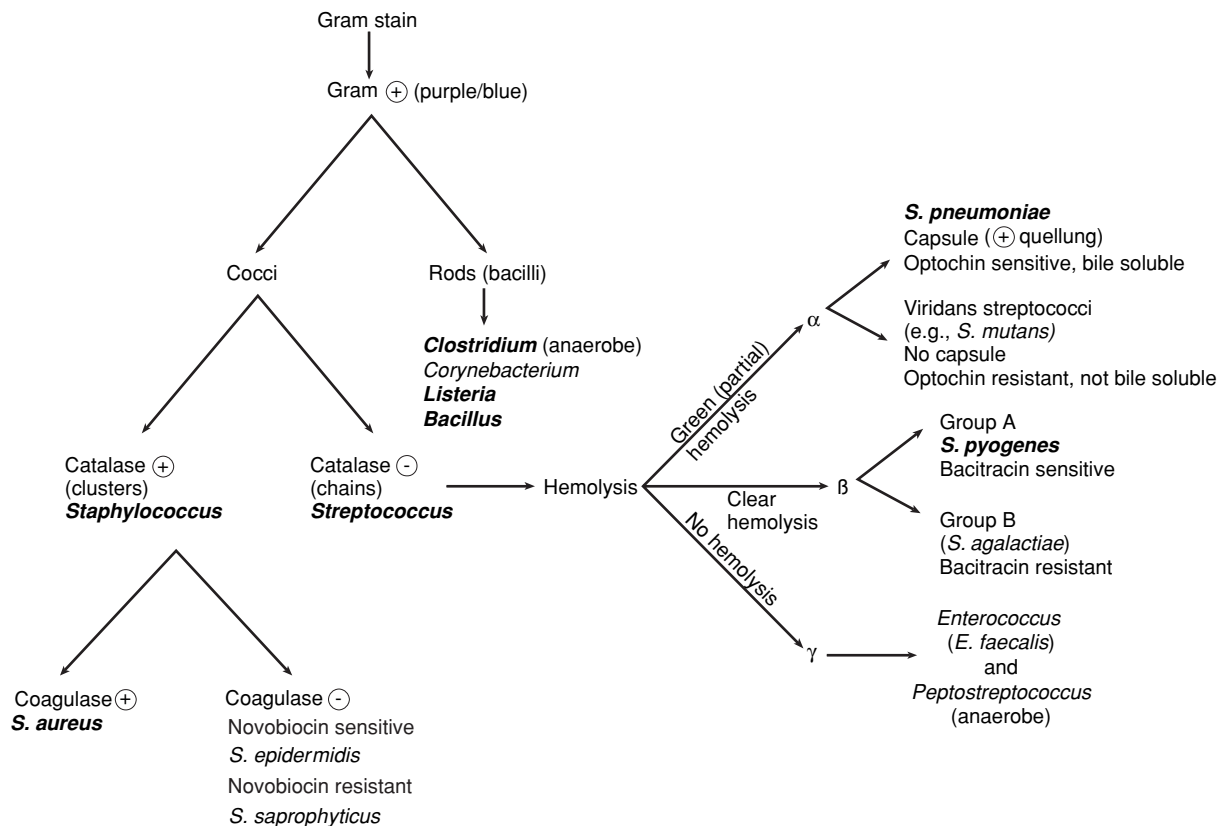


(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:39.)

Gram stain limitations	<p>These bugs do not Gram stain well:</p> <p><i>Treponema</i> (too thin to be visualized).</p> <p><i>Rickettsia</i> (intracellular parasite).</p> <p>Mycobacteria (high-lipid-content cell wall requires acid-fast stain).</p> <p><i>Mycoplasma</i> (no cell wall).</p> <p><i>Legionella pneumophila</i> (primarily intracellular).</p> <p><i>Chlamydia</i> (intracellular parasite).</p>	<p>These Rascals May Microscopically Lack Color.</p> <p>Treponemes—darkfield microscopy and fluorescent antibody staining.</p> <p>Mycobacteria—acid fast.</p> <p><i>Legionella</i>—silver stain.</p>
Fermentation patterns of <i>Neisseria</i>	The pathogenic <i>Neisseria</i> species are differentiated on the basis of sugar fermentation (see Color Image 4).	<p>MenGococci ferment Maltose and Glucose.</p> <p>Gonococci ferment Glucose.</p>
Pigment-producing bacteria	<p><i>S. aureus</i> produces a yellow pigment.</p> <p><i>Pseudomonas aeruginosa</i> produces a blue-green pigment.</p> <p><i>Serratia marcescens</i> produces a red pigment.</p>	<p><i>Aureus</i> (Latin) = gold.</p> <p><i>Serratia marcescens</i> = maraschino cherries are red.</p>
IgA proteases	IgA proteases allow these organisms to colonize mucosal surfaces: <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>N. gonorrhoeae</i> , <i>Haemophilus influenzae</i> .	

► MICROBIOLOGY AND IMMUNOLOGY—CLINICAL BACTERIOLOGY (*continued*)

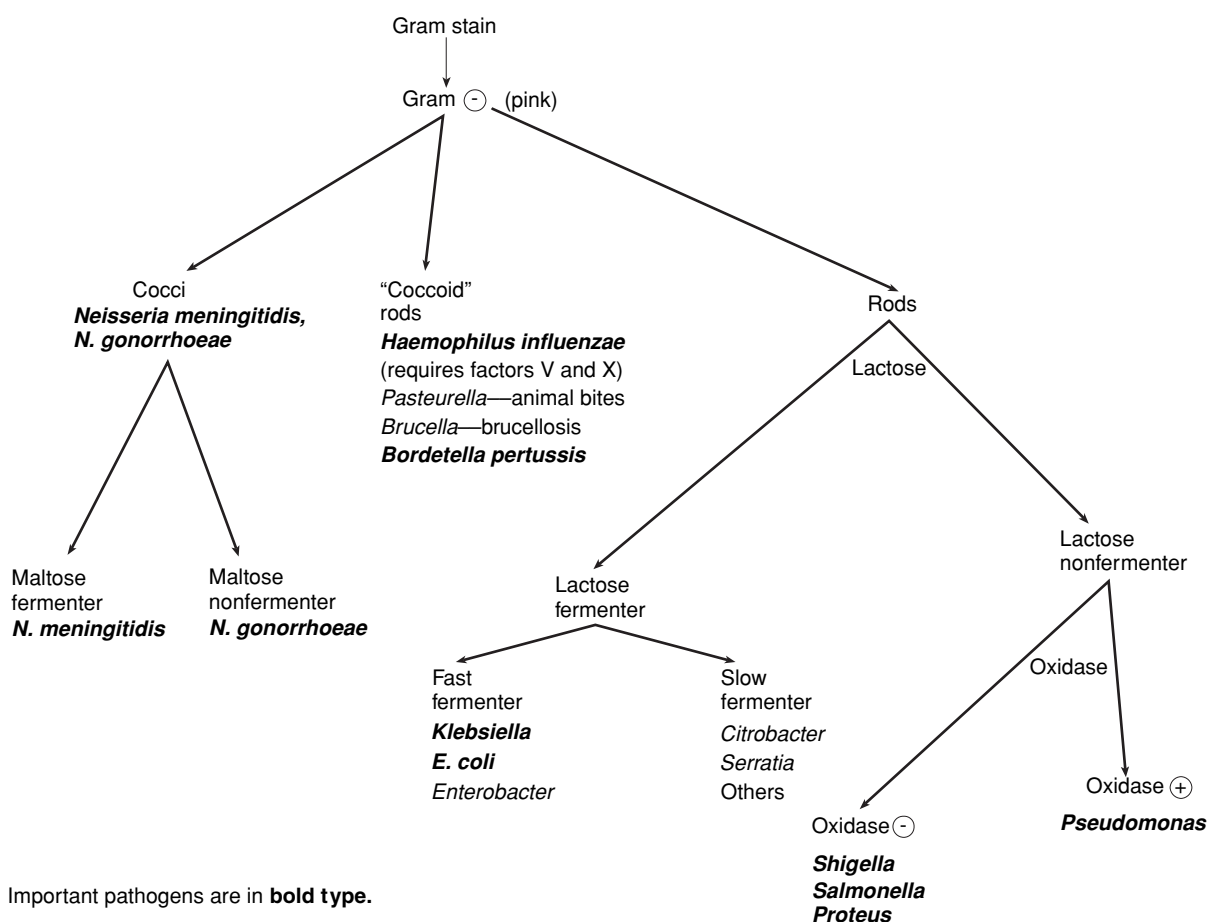
Gram-positive lab algorithm



Important pathogens are in **bold type**.

Note: *Enterococcus* is either α - or γ -hemolytic.

Gram-negative lab algorithm



Special culture requirements

Bug	Media used for isolation
<i>H. influenzae</i>	Chocolate agar with factors V (NAD) and X (hematin)
<i>N. gonorrhoeae</i>	Thayer-Martin (VCN) media
<i>B. pertussis</i>	Bordet-Gengou (potato) agar
<i>C. diphtheriae</i>	Tellurite plate, Löffler's medium, blood agar
<i>M. tuberculosis</i>	Löwenstein-Jensen agar
Lactose-fermenting enterics	Pink colonies on MacConkey's agar
<i>Legionella</i>	Charcoal yeast extract agar buffered with increased iron and cysteine
Fungi	Sabouraud's agar

Stains

Congo red	Amyloid; apple-green birefringence in polarized light (because of β -pleated sheets).
Giemsa's	<i>Borrelia</i> , <i>Plasmodium</i> , trypanosomes, <i>Chlamydia</i> .
PAS (periodic acid-Schiff)	Stains glycogen, mucopolysaccharides; used to diagnose Whipple's disease.
Ziehl-Neelsen	Acid-fast bacteria.
India ink	<i>Cryptococcus neoformans</i> .
Silver stain	Fungi, PCP, <i>Legionella</i> .

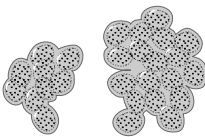
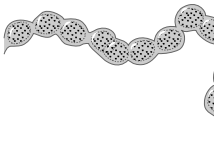
► MICROBIOLOGY AND IMMUNOLOGY—CLINICAL BACTERIOLOGY (*continued*)**Conjugation, transduction, and transformation**

Transfer procedure	Transfer process	Types of cells involved	Nature of DNA transferred
Conjugation	DNA transferred from 1 bacterium to another	Prokaryotic	Chromosomal or plasmid
Transduction	DNA transferred by a virus from 1 cell to another	Prokaryotic	Any gene in generalized transduction; only certain genes in specialized transduction
Transformation	Purified DNA taken up by a cell	Prokaryotic or eukaryotic (e.g., human)	Any DNA

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:19.)

► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY		
Obligate aerobes	Use an O ₂ -dependent system to generate ATP. Examples include <i>Nocardia</i> , <i>Pseudomonas aeruginosa</i> , <i>Mycobacterium tuberculosis</i> , and <i>Bacillus</i> . <i>M. tuberculosis</i> has a predilection for the apices of the lung, which have the highest PO ₂ .	<i>P. AERuginosa</i> is an AERobe seen in burn wounds, nosocomial pneumonia, and pneumonias in cystic fibrosis patients. Nagging Pests Must Breathe.
Obligate anaerobes	Examples include <i>Clostridium</i> , <i>Bacteroides</i> , and <i>Actinomyces</i> . They lack catalase and/or superoxide dismutase and thus are susceptible to oxidative damage. They are generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO ₂ and H ₂).	Anaerobes are normal flora in GI tract, pathogenic elsewhere. AminO ₂ glycosides are ineffective against anaerobes because these antibiotics require O ₂ to enter into bacterial cell.
Intracellular bugs		
Obligate intracellular	<i>Rickettsia</i> , <i>Chlamydia</i> . Can't make own ATP.	Stay inside (cells) when it is Really Cold.
Facultative intracellular	<i>Salmonella</i> , <i>Neisseria</i> , <i>Brucella</i> , <i>Mycobacterium</i> , <i>Listeria</i> , <i>Francisella</i> , <i>Legionella</i> , <i>Yersinia</i> .	Some Nasty Bugs May Live FacultativeLY.
Encapsulated bacteria	Examples are <i>Streptococcus pneumoniae</i> (pneumococcus), <i>Haemophilus influenzae</i> (especially B serotype), <i>Neisseria meningitidis</i> (meningococcus), and <i>Klebsiella pneumoniae</i> . Polysaccharide capsule is an antiphagocytic virulence factor. Positive quellung reaction—if encapsulated bug is present, capsule swells when specific anticapsular antisera are added.	IgG ₂ necessary for immune response. Capsule serves as antigen in vaccines (Pneumovax, <i>H. influenzae</i> B, meningococcal vaccines). Quellung = capsular “swellung.”
Spores: bacterial	Only certain gram-positive rods form spores when nutrients are limited. Spores are highly resistant to destruction by heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to kill spores (as is done to surgical equipment).	Gram-positive soil bugs ≈ spore formers (<i>Bacillus anthracis</i> , <i>Clostridium perfringens</i> , <i>C. tetani</i>).
α-hemolytic bacteria	Include the following organisms: 1. <i>Streptococcus pneumoniae</i> (catalase negative and optochin sensitive) (see Color Image 1) 2. Viridans streptococci (catalase negative and optochin resistant)	
β-hemolytic bacteria	Include the following organisms: 1. <i>Staphylococcus aureus</i> (catalase and coagulase positive) 2. <i>Streptococcus pyogenes</i> (catalase negative and bacitracin sensitive) 3. <i>Streptococcus agalactiae</i> (catalase negative and bacitracin resistant) 4. <i>Listeria monocytogenes</i> (tumbling motility, meningitis in newborns, unpasteurized milk)	

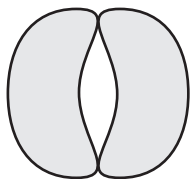
► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY (continued)

Catalase/coagulase (gram-positive cocci)	Catalase degrades H_2O_2 , an antimicrobial product of PMNs. H_2O_2 is a substrate for myeloperoxidase. Staphylococci make catalase, whereas streptococci do not. <i>S. aureus</i> makes coagulase, whereas <i>S. epidermidis</i> and <i>S. saprophyticus</i> do not.	Staph make catalase because they have more “staff.” Bad staph (<i>aureus</i> , because <i>epidermidis</i> is skin flora) make coagulase and toxins.
<i>Staphylococcus aureus</i> 	Protein A (virulence factor) binds Fc-IgG, inhibiting complement fixation and phagocytosis. Causes: <ol style="list-style-type: none"> 1. Inflammatory disease—skin infections, organ abscesses, pneumonia 2. Toxin-mediated disease—toxic shock syndrome (TSST-1 toxin), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins) (see Color Image 3) 	TSST is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation. <i>S. aureus</i> food poisoning is due to ingestion of preformed toxin. Causes acute bacterial endocarditis.
<i>Streptococcus pyogenes</i> (group A β-hemolytic streptococci) sequelae	Causes: <ol style="list-style-type: none"> 1. Pyogenic—pharyngitis, cellulitis, impetigo 2. Toxigenic—scarlet fever, toxic shock syndrome 3. Immunologic—rheumatic fever, acute glomerulonephritis Bacitracin sensitive. Antibody to M protein enhances host defenses against <i>S. pyogenes</i> . ASO titer detects recent <i>S. pyogenes</i> infection.	PH aryngitis gives you rheumatic “ PH ever” and glomerulone PH ritis. No “ rheum ” for SPECC ulation: Subcutaneous nodules, Polyarthriti s , Erythema marginatum, Chorea, Carditis.
<i>Streptococcus pneumoniae</i>	Most common cause of: Meningitis Otitis media Pneumonia Sinusitis Encapsulated. IgA protease.	<i>S. pneumoniae</i> MOPS are Most OP tochin Sensitive. Pneumococcus is associated with “rusty” sputum, sepsis in sickle cell anemia, and splenectomy.
Group B streptococci	Bacitracin resistant, β -hemolytic; cause pneumonia, meningitis, and sepsis, mainly in babies.	
Enterococci 	Enterococci (<i>Enterococcus faecalis</i> and <i>E. faecium</i>) are penicillin G resistant and cause UTI and subacute endocarditis. Lancefield group D includes the enterococci and the nonenterococcal group D streptococci. Lancefield grouping is based on differences in the C carbohydrate on the bacterial cell wall. Variable hemolysis.	Enterococci, harder than nonenterococcal group D, can thus grow in 6.5% NaCl (lab test). <i>Entero</i> = intestine, <i>faecalis</i> = feces, <i>strepto</i> = twisted (chains), <i>coccus</i> = berry.

Viridans group streptococci	Viridans streptococci are α -hemolytic. They are normal flora of the oropharynx and cause dental caries (<i>Streptococcus mutans</i>) and subacute bacterial endocarditis (<i>S. sanguis</i>). Resistant to optochin, differentiating them from <i>S. pneumoniae</i> , which is α -hemolytic but is optochin sensitive.	<i>Sanguis</i> (Latin) = blood. There is lots of blood in the heart (endocarditis). Viridans group strep live in the mouth because they are not afraid of-the-chin (op-to-chin resistant).
Clostridia (with exotoxins)	Gram-positive, spore-forming, obligate anaerobic bacilli. <i>Clostridium tetani</i> produces an exotoxin causing tetanus. <i>C. botulinum</i> produces a preformed, heat-labile toxin that inhibits ACh release, causing botulism. <i>C. perfringens</i> produces α toxin (lecithinase) that causes myonecrosis, gas gangrene, or hemolysis. <i>C. difficile</i> produces a cytotoxin, an exotoxin that kills enterocytes, causing pseudomembranous colitis. Often 2° to antibiotic use, especially clindamycin or ampicillin.	TET anus is TET anic paralysis (blocks glycine release [inhibitory neurotransmitter]) from Renshaw cells in spinal cord. BOT ulinum is from bad BOT tles of food (causes a flaccid paralysis). PER fringens PER forates a gangrenous leg. DI fficile causes DI arrhea. Treat with metronidazole.
Diphtheria (and exotoxin)	Caused by <i>Corynebacterium diphtheriae</i> via exotoxin encoded by β -prophage. Potent exotoxin inhibits protein synthesis via ADP ribosylation of EF-2. Symptoms include pseudomembranous pharyngitis (grayish-white membrane) with lymphadenopathy. Lab diagnosis based on gram-positive rods with metachromatic granules.	<i>Coryne</i> = club shaped. Grows on tellurite agar. ABCDEFGF : ADP ribosylation Beta-prophage <i>Corynebacterium</i> <i>Diphtheriae</i> Elongation Factor 2 Granules
Anthrax	Caused by <i>Bacillus anthracis</i> , a gram-positive, spore-forming rod that produces anthrax toxin. Contact → malignant pustule (painless ulcer); can progress to bacteremia and death. Inhalation of spores → flulike symptoms that rapidly progress to fever, pulmonary hemorrhage, and shock.	Black skin lesions—vesicular papules covered by black eschar. Woolsorters' disease—inhalation of spores from contaminated wool.
Actinomyces vs. Nocardia	Both are gram-positive rods forming long branching filaments resembling fungi. <i>Actinomyces israelii</i> , a gram-positive anaerobe, causes oral/facial abscesses with "sulfur granules" that may drain through sinus tracts in skin. Normal oral flora. <i>Nocardia asteroides</i> , a gram-positive and also a weakly acid-fast aerobe in soil, causes pulmonary infection in immunocompromised patients.	<i>A. israelii</i> forms yellow "sulfur granules" in sinus tracts. SNAP : Sulfa for <i>Nocardia</i> ; <i>Actinomyces</i> use Penicillin

► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY (*continued*)**Penicillin and gram-negative bugs**

Gram-negative bugs are resistant to benzyl penicillin G but may be susceptible to penicillin derivatives such as ampicillin. The gram-negative outer membrane layer inhibits entry of penicillin G and vancomycin.

Neisseria

Gram-negative cocci.

Gonococci

No polysaccharide capsule

No maltose fermentation

No vaccine

Causes gonorrhea, septic arthritis, neonatal conjunctivitis, PID

Meningococci

Polysaccharide capsule

Maltose fermentation

Vaccine

Causes meningococemia and meningitis, Waterhouse-Friderichsen syndrome

Haemophilus influenzae

HaEMOPhilus causes Epiglottitis, Meningitis, Otitis media, and Pneumonia. Small gram-negative (coccobacillary) rod. Aerosol transmission. Most invasive disease caused by capsular type B. Produces IgA protease. Culture on chocolate agar requires factors V (NAD) and X (hematin) for growth. Treat meningitis with ceftriaxone. Rifampin prophylaxis in close contacts. Does not cause the flu (influenza virus does).

When a child has “flu,” mom goes to five (V) and dime (X) store to buy some chocolate. Vaccine contains type B capsular polysaccharide conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Enterobacteriaceae

Diverse family including *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*. All species have somatic (O) antigen (which is the polysaccharide of endotoxin). The capsular (K) antigen is related to the virulence of the bug. The flagellar (H) antigen is found in motile species. All ferment glucose and are oxidase negative.

Think COFFEE:

Capsular

O antigen

Flagellar antigen

Ferment glucose

Enterobacteriaceae

Lactose-fermenting enteric bacteria

These bacteria grow pink colonies on MacConkey's agar. Examples include *Klebsiella*, *E. coli*, *Enterobacter*, and *Citrobacter*.

Lactose is **KEE**.

Salmonella* vs. *Shigella

Both are non-lactose fermenters; both invade intestinal mucosa and can cause bloody diarrhea. Only *SalMONella* is Motile and can invade further and disseminate hematogenously. Symptoms of salmonellosis may be prolonged with antibiotic treatments, and there is typically a monocyte response. *Shigella* is more virulent (10^1 organisms) than *Salmonella* (10^5 organisms).

Salmon swim (motile and disseminate). *Salmonella* has an animal reservoir; *Shigella* does not and is transmitted via “Food, Fingers, Feces, and Flies.”

Yersinia enterocolitica

Usually transmitted from pet feces (e.g., puppies), contaminated milk, or pork. Outbreaks are common in day-care centers. Can mimic Crohn's or appendicitis; can disseminate to produce lymphadenitis.

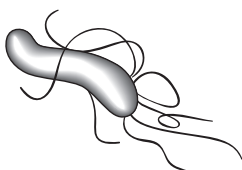
Bugs causing food poisoning	<p><i>Vibrio parahaemolyticus</i> and <i>V. vulnificus</i> in contaminated seafood.</p> <p><i>Bacillus cereus</i> in reheated rice.</p> <p><i>S. aureus</i> in meats, mayonnaise, custard.</p> <p><i>Clostridium perfringens</i> in reheated meat dishes.</p> <p><i>C. botulinum</i> in improperly canned foods (bulging cans).</p> <p><i>E. coli</i> O157:H7 in undercooked meat.</p> <p><i>Salmonella</i> in poultry, meat, and eggs.</p>	<p><i>S. aureus</i> food poisoning starts quickly and ends quickly.</p> <p>“Food poisoning from reheated rice? Be serious!” (<i>B. cereus</i>).</p>																															
Bugs causing diarrhea	<table><tr><th>Type</th><th>Species</th></tr><tr><td rowspan="10">Bloody diarrhea</td><td><i>Campylobacter</i></td></tr><tr><td><i>Salmonella</i></td></tr><tr><td><i>Shigella</i></td></tr><tr><td>Enterohemorrhagic <i>E. coli</i></td></tr><tr><td>Enteroinvasive <i>E. coli</i></td></tr><tr><td><i>Yersinia enterocolitica</i></td></tr><tr><td><i>C. difficile</i></td></tr><tr><td><i>Entamoeba histolytica</i></td></tr><tr><td>Enterotoxigenic <i>E. coli</i></td></tr><tr><td><i>Vibrio cholerae</i></td></tr><tr><td rowspan="3">Watery diarrhea</td><td><i>C. perfringens</i></td></tr><tr><td>Protozoa</td></tr><tr><td>Viruses</td></tr></table>	Type	Species	Bloody diarrhea	<i>Campylobacter</i>	<i>Salmonella</i>	<i>Shigella</i>	Enterohemorrhagic <i>E. coli</i>	Enteroinvasive <i>E. coli</i>	<i>Yersinia enterocolitica</i>	<i>C. difficile</i>	<i>Entamoeba histolytica</i>	Enterotoxigenic <i>E. coli</i>	<i>Vibrio cholerae</i>	Watery diarrhea	<i>C. perfringens</i>	Protozoa	Viruses	<table><tr><th>Findings</th></tr><tr><td>Comma- or S-shaped organisms; growth at 42°C; oxidase positive</td></tr><tr><td>Motile</td></tr><tr><td>Nonmotile; very low ID₅₀; causes dysentery</td></tr><tr><td>Shiga-like toxin; can cause HUS</td></tr><tr><td>O157:H7; invades colonic mucosa</td></tr><tr><td>Day-care outbreaks, pseudoappendicitis</td></tr><tr><td>Pseudomembranous colitis</td></tr><tr><td>Protozoan</td></tr><tr><td>Traveler’s diarrhea; no preformed toxin</td></tr><tr><td>Comma-shaped organisms; rice-water stools</td></tr><tr><td>Also causes gas gangrene</td></tr><tr><td><i>Giardia</i>, <i>Cryptosporidium</i> (in immunocompromised)</td></tr><tr><td>Rotavirus, adenovirus, Norwalk virus</td></tr></table>	Findings	Comma- or S-shaped organisms; growth at 42°C; oxidase positive	Motile	Nonmotile; very low ID ₅₀ ; causes dysentery	Shiga-like toxin; can cause HUS	O157:H7; invades colonic mucosa	Day-care outbreaks, pseudoappendicitis	Pseudomembranous colitis	Protozoan	Traveler’s diarrhea; no preformed toxin	Comma-shaped organisms; rice-water stools	Also causes gas gangrene	<i>Giardia</i> , <i>Cryptosporidium</i> (in immunocompromised)	Rotavirus, adenovirus, Norwalk virus
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Cholera and pertussis toxins	<p><i>Vibrio cholerae</i> toxin permanently activates G_s, causing rice-water diarrhea.</p> <p>Pertussis toxin permanently disables G_i, causing whooping cough.</p> <p>Both toxins act via ADP ribosylation that permanently activates adenyl cyclase (↑ cAMP).</p>	<p>Cholera turns the “on” on.</p> <p>Pertussis turns the “off” off.</p> <p>Pertussis toxin also promotes lymphocytosis by inhibiting chemokine receptors.</p>																															
<i>Legionella pneumophila</i>	<p>Legionnaires’ disease. Gram-negative rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract culture with iron and cysteine.</p> <p>Aerosol transmission from environmental water source habitat. No person-to-person transmission. Treat with erythromycin.</p>	<p>Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no sissy (cysteine).</p>																															

► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY (*continued*)***Pseudomonas aeruginosa***

PSEUDO*monas* is associated with wound and burn infections, **P**neumonia (especially in cystic fibrosis), **S**epsis (black lesions on skin), **E**xternal otitis (swimmer's ear), **U**TI, **D**rug use and **D**iabetic **O**steomyelitis, and hot tub folliculitis. Aerobic gram-negative rod. Non-lactose fermenting, oxidase positive. Produces pyocyanin (blue-green) pigment. Water source. Produces endotoxin (fever, shock) and exotoxin A (inactivates EF-2). Treat with aminoglycoside plus extended-spectrum penicillin (e.g., piperacillin, ticarcillin).

AERuginosa—**AER**obic.

Think water connection and blue-green pigment.
Think *Pseudomonas* in burn victims.

Helicobacter pylori

Causes gastritis and up to 90% of duodenal ulcers. Risk factor for peptic ulcer and gastric carcinoma. Gram-negative rod. Urease positive (e.g., urease breath test). Creates alkaline environment. Treat with triple therapy: (1) bismuth (Pepto-Bismol), metronidazole, and either tetracycline or amoxicillin; or (2) (more costly) metronidazole, omeprazole, and clarithromycin.

Pylori—think pylorus of stomach. *Proteus* and *H. pylori* are both urease positive (cleave urea to ammonia).

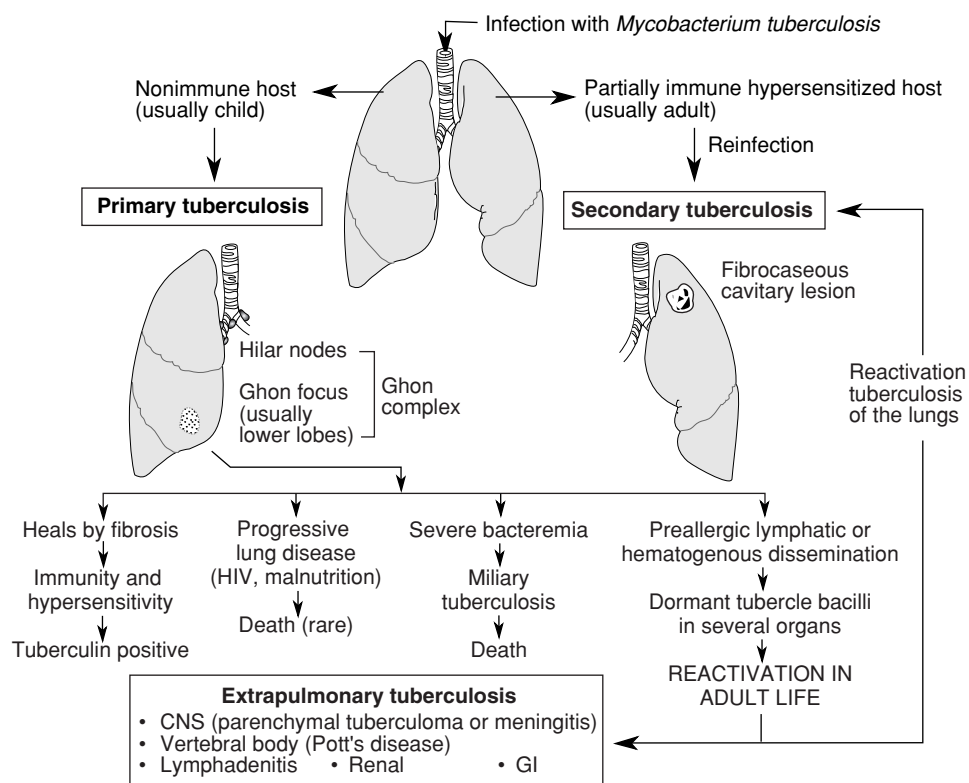
Zoonotic bacteria

Species	Disease	Transmission and source	
<i>Borrelia burgdorferi</i>	Lyme disease	Tick bite; <i>Ixodes</i> ticks that live on deer and mice	Bugs From Your Pet Undulate and
<i>Brucella</i> spp.	Brucellosis/ Undulant fever	Dairy products, contact with animals	Unpasteurized dairy products give you Undulant fever.
<i>Francisella tularensis</i>	Tularemia	Tick bite; rabbits, deer	
<i>Yersinia pestis</i>	Plague	Flea bite; rodents, especially prairie dogs	
<i>Pasteurella multocida</i>	Cellulitis	Animal bite; cats, dogs	

Gardnerella vaginalis

A pleomorphic, gram-variable rod that causes vaginosis—greenish vaginal discharge with fishy smell; nonpainful. *Mobiluncus*, an anaerobe, is also involved. Treat with metronidazole. Clue cells, or vaginal epithelial cells covered with bacteria, are visible under the microscope.

1° and 2° tuberculosis



(Adapted, with permission, from Chandrasoma P, Taylor CR. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:523.)

Ghon complex

TB granulomas (Ghon focus) with lobar and perihilar lymph node involvement. Reflects 1° infection or exposure.

Mycobacteria

Mycobacterium tuberculosis (TB, often resistant to multiple drugs).
M. kansasii (pulmonary TB-like symptoms).
M. scrofulaceum (cervical lymphadenitis in kids).
M. avium-intracellulare (often resistant to multiple drugs; causes disseminated disease in AIDS).
 All mycobacteria are acid-fast organisms.

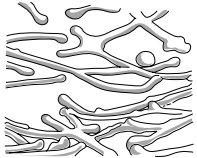
TB symptoms include fever, night sweats, weight loss, and hemoptysis (see Color Image 2).

Leprosy (Hansen's disease)

Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves) and cannot be grown in vitro. Reservoir in United States: armadillos.
 Treatment: long-term oral dapsone; toxicity is hemolysis and methemoglobinemia.
 Alternate treatments include rifampin and combination of clofazimine and dapsone.

Hansen's disease has 2 forms: lepromatous and tuberculoid; lepromatous is worse (failed cell-mediated immunity); tuberculoid is self-limited.
LEpromatous = **LE**thal.

► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY (*continued*)

Rickettsiae	Rickettsiae are obligate intracellular parasites and need CoA and NAD. All except <i>Coxiella</i> are transmitted by an arthropod vector and cause headache, fever, and rash; <i>Coxiella</i> is an atypical rickettsia because it is transmitted by aerosol and causes pneumonia. Tetracycline is the treatment of choice for most rickettsial infections.	Classic triad—headache, fever, rash (vasculitis).
Rickettsial diseases and vectors	Rocky Mountain spotted fever (tick)— <i>Rickettsia rickettsii</i> . Endemic typhus (fleas)— <i>R. typhi</i> . Epidemic typhus (human body louse)— <i>R. prowazekii</i> . Q fever (inhaled aerosols)— <i>Coxiella burnetii</i> . Treatment for all: tetracycline.	TyPHus has centriPHugal (outward) spread of rash; sPotted fever is centriPetal (inward). Q fever is Q ueer because it has no rash, has no vector, and has negative Weil-Felix, and its causative organism can survive outside for a long time and does not have <i>Rickettsia</i> as its genus name.
Rocky Mountain spotted fever	Caused by <i>Rickettsia rickettsii</i> . Symptoms: rash on palms and soles (migrating to wrists, ankles, then trunk), headache, fever. Endemic to East Coast (in spite of name).	Palm and sole rash is seen in Rocky Mountain spotted fever, syphilis, and coxsackievirus A infection (hand, foot, and mouth disease).
Weil-Felix reaction	Weil-Felix reaction assays for antirickettsial antibodies, which cross-react with <i>Proteus</i> antigen. Weil-Felix is usually positive for typhus and Rocky Mountain spotted fever but negative for Q fever.	
<i>Mycoplasma pneumoniae</i> 	Classic cause of atypical “walking” pneumonia (insidious onset, headache, nonproductive cough, diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM). Grown on Eaton’s agar. Treatment: tetracycline or erythromycin (bugs are penicillin resistant because they have no cell wall).	No cell wall. Only bacterial membrane containing cholesterol. <i>Mycoplasma pneumoniae</i> is more common in patients < 30 years of age. Frequent outbreaks in military recruits and prisons.

► MICROBIOLOGY AND IMMUNOLOGY—BACTERIOLOGY (*continued*)**Chlamydiae**

Chlamydiae are obligate intracellular parasites that cause mucosal infections. 2 forms:

1. Elementary body (small, dense), which Enters cell via endocytosis
2. Initial or Reticulate body, which Replicates in cell by fission

Chlamydia trachomatis causes reactive arthritis, conjunctivitis, and nongonococcal urethritis.

C. pneumoniae and *C. psittaci* cause atypical pneumonia; transmitted by aerosol.

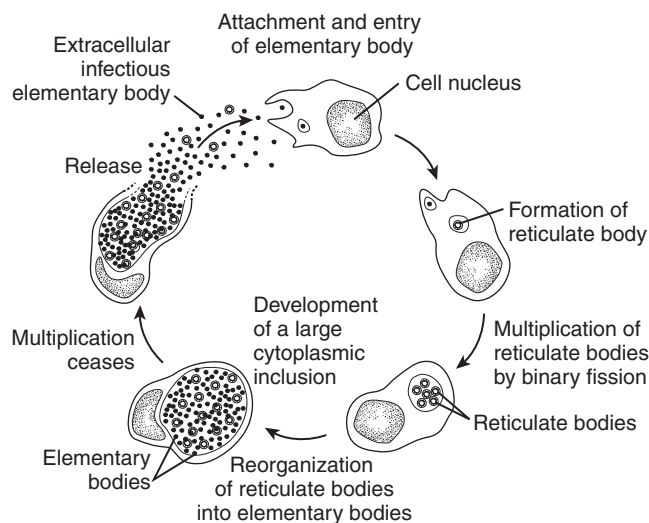
Treatment: erythromycin or tetracycline.

Chlamys = cloak (intracellular).

Chlamydia psittaci—notable for an avian reservoir.

The chlamydial peptidoglycan wall is unusual in that it lacks muramic acid.

Lab diagnosis: cytoplasmic inclusions seen on Giemsa or fluorescent antibody-stained smear.

***Chlamydia trachomatis* serotypes**

Types A, B, and C—chronic infection, cause blindness in Africa.

Types D–K—urethritis/PID, ectopic pregnancy, neonatal pneumonia, or neonatal conjunctivitis.

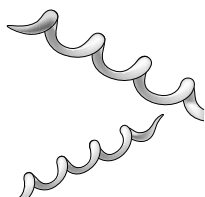
Types L1, L2, and L3—lymphogranuloma venereum (acute lymphadenitis—positive Frei test).

ABC = Africa/Blindness/Chronic infection.

L1–3 = Lymphogranuloma venereum.

D–K = everything else.

Neonatal disease acquired by passage through infected birth canal. Treat with erythromycin eye drops.

Spirochetes

The spirochetes are spiral-shaped bacteria with axial filaments and include *Borrelia* (big size), *Leptospira*, and *Treponema*. Only *Borrelia* can be visualized using aniline dyes (Wright's or Giemsa stain) in light microscopy. *Treponema* is visualized by dark-field microscopy.

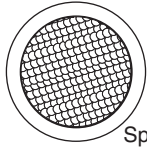

BLT. B is Big.

Lyme disease	<p>Caused by <i>Borrelia burgdorferi</i>, which is transmitted by the tick <i>Ixodes</i>.</p> <p>Classic symptom is erythema chronicum migrans, an expanding “bull’s eye” red rash with central clearing. Also affects joints, CNS, and heart.</p> <p>Mice are important reservoirs. Deer required for tick life cycle.</p> <p>Treat with tetracycline.</p> <p>Named after Lyme, Connecticut; disease is common in northeastern United States.</p> <p>Transmission is most common in summer months.</p>	<p>3 stages of Lyme disease:</p> <p>Stage 1—erythema chronicum migrans, flulike symptoms.</p> <p>Stage 2—neurologic and cardiac manifestations.</p> <p>Stage 3—autoimmune migratory polyarthritis.</p> <p>BAKE a Key Lyme pie: Bell’s palsy, Arthritis, Kardiac block, Erythema chronicum migrans.</p>												
Treponemal disease	<p>Treponemes are spirochetes.</p> <p><i>Treponema pallidum</i> causes syphilis.</p> <p><i>T. pertenue</i> causes yaws (a tropical infection that is not an STD, although VDRL test is positive).</p>													
Syphilis 1° syphilis 2° syphilis 3° syphilis Congenital syphilis	<p>Caused by spirochete <i>Treponema pallidum</i>.</p> <p>Presents with painless chancre (localized disease).</p> <p>Disseminated disease with constitutional symptoms, maculopapular rash (palms and soles), condylomata lata.</p> <p>Gummas, aortitis, neurosyphilis (tabes dorsalis), Argyll Robertson pupil (see Color Image 12).</p> <p>Saber shins, saddle nose, deafness.</p>	<p>Treat with penicillin G.</p> <p>Secondary syphilis = Systemic.</p> <p>Signs: broad-based ataxia, positive Romberg, Charcot joints, stroke without hypertension.</p>												
Argyll Robertson pupil	<p>Argyll Robertson pupil constricts with accommodation but is not reactive to light. Pathognomonic for 3° syphilis.</p>	<p>“Prostitute’s pupil”—accommodates but does not react.</p>												
VDRL vs. FTA-ABS	<p>FTA-ABS is specific for treponemes, turns positive earliest in disease, and remains positive longest.</p> <table> <thead> <tr> <th>VDRL</th> <th>FTA</th> <th>Interpretation</th> </tr> </thead> <tbody> <tr> <td>+</td> <td>+</td> <td>Active infection</td> </tr> <tr> <td>+</td> <td>–</td> <td>Probably false positive</td> </tr> <tr> <td>–</td> <td>+</td> <td>Successfully treated</td> </tr> </tbody> </table>	VDRL	FTA	Interpretation	+	+	Active infection	+	–	Probably false positive	–	+	Successfully treated	<p>FTA-ABS = Find The Antibody-ABSolutely:</p> <ol style="list-style-type: none"> 1. Most specific 2. Earliest positive 3. Remains positive the longest
VDRL	FTA	Interpretation												
+	+	Active infection												
+	–	Probably false positive												
–	+	Successfully treated												
VDRL false positives	<p>VDRL detects nonspecific antibody that reacts with beef cardiolipin. Used for diagnosis of syphilis, but many biologic false positives, including viral infection (mononucleosis, hepatitis), some drugs, rheumatic fever, rheumatoid arthritis, SLE, and leprosy.</p>	<p>VDRL:</p> <p>Viruses (mono, hepatitis)</p> <p>Drugs</p> <p>Rheumatic fever and rheumatic arthritis</p> <p>Lupus and leprosy</p>												

► MICROBIOLOGY AND IMMUNOLOGY—MYCOLOGY

Spores: fungal	Most fungal spores are asexual. Both coccidioidomycosis and histoplasmosis are transmitted by inhalation of asexual spores.	Conidia—asexual fungal spores (e.g., blastoconidia, arthroconidia).
<i>Candida albicans</i>	Systemic or superficial fungal infection (budding yeast with pseudohyphae in culture at 20°C; germ tube formation at 37°C). Thrush esophagitis with immunocompromised patients (neonates, steroids, diabetes, AIDS), endocarditis in IV drug users, vaginitis (post-antibiotic), diaper rash. Treatment: nystatin for superficial infection; amphotericin B for serious systemic infection.	<i>Alba</i> = white.

Systemic mycoses

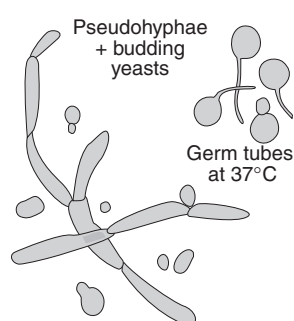
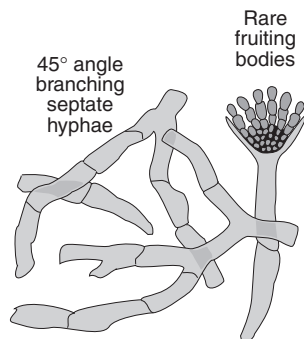
Disease	Endemic location	Notes
Coccidioidomycosis	Southwestern United States, California.	San Joaquin Valley or desert (desert bumps) “valley fever” (see Color Image 7)
 Spherule filled with endospores		
Histoplasmosis	Mississippi and Ohio river valleys.	Bird or bat droppings; intracellular (tiny yeast inside macrophages)
Paracoccidioidomycosis	Rural Latin America.	“Captain’s wheel” appearance
Blastomycosis	States east of Mississippi River and Central America.	Big, Broad-Based Budding
 Broad-based budding	All of the above are caused by dimorphic fungi, which are mold in soil (at lower temperature) and yeast in tissue (at higher/body temperature: 37°C) except coccidioidomycosis, which is a spherule in tissue. Treat with fluconazole or ketoconazole for local infection; amphotericin B for systemic infection. Systemic mycoses can mimic TB (granuloma formation).	Cold = Mold Heat = Yeast Culture on Sabouraud’s agar

Cutaneous mycoses

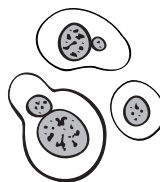
Tinea versicolor	Caused by <i>Malassezia furfur</i> . Causes hypopigmented skin lesions. Occurs in hot, humid weather. Treat with topical miconazole, selenium sulfide (Selsun).
Tinea nigra	Caused by <i>Cladosporium werneckii</i> . Infection of keratinized layer of skin. Appears as brownish spot. Treat with topical salicylic acid.
Tinea pedis, tinea cruris, tinea corporis, tinea capitis	Pruritic lesions with central clearing resembling a ring, caused by dermatophytes (<i>Microsporum</i> , <i>Trichophyton</i> , and <i>Epidermophyton</i>). See mold hyphae in KOH prep, not dimorphic. Pets are a reservoir for <i>Microsporum</i> and can be treated with topical azoles.

Opportunistic fungal infections

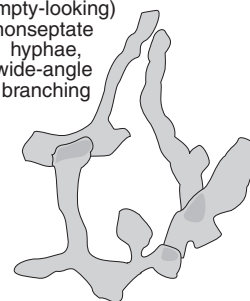
<i>Candida albicans</i>	Thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (high pH, diabetes, use of antibiotics), disseminated candidiasis (to any organ), chronic mucocutaneous candidiasis (see Color Image 9).
<i>Aspergillus fumigatus</i>	Allergic bronchopulmonary aspergillosis, lung cavity aspergilloma (“fungus ball”), invasive aspergillosis. Mold with septate hyphae that branch at a V-shaped (45°) angle. Not dimorphic.
<i>Cryptococcus neoformans</i>	Cryptococcal meningitis, cryptococcosis. Heavily encapsulated yeast . Not dimorphic. Found in soil, pigeon droppings. Culture on Sabouraud’s agar. Stains with India ink. Latex agglutination test detects polysaccharide capsular antigen (see Color Image 8).
<i>Mucor</i> and <i>Rhizopus</i> spp.	Mucormycosis. Mold with irregular nonseptate hyphae branching at wide angles ($\geq 90^\circ$). Disease mostly in ketoacidotic diabetic and leukemic patients. Fungi also proliferate in the walls of blood vessels and cause infarction of distal tissue. Rhinocerebral, frontal lobe abscesses.

*Candida**Aspergillus*

5–10-μm yeasts with wide capsular halo
Narrow-based unequal budding

*Cryptococcus*

Irregular broad (empty-looking) nonseptate hyphae, wide-angle branching

*Mucor****Pneumocystis carinii***

Causes diffuse interstitial pneumonia (PCP). Yeast (originally classified as protozoan). Inhaled. Most infections asymptomatic. Immunosuppression (e.g., AIDS) predisposes to disease. Diagnosed by lung biopsy or lavage. Identified by methenamine silver stain of lung tissue. Treat with TMP-SMX, pentamidine, dapsone. Start prophylaxis when CD4 drops < 200 cells/mL in HIV patients (see Color Image 17).

Sporothrix schenckii

Sporotrichosis. Dimorphic fungus that lives on vegetation. When traumatically introduced into the skin, typically by a thorn (“rose gardener’s” disease), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis). Little systemic illness. Cigar-shaped budding yeast visible in pus. Treat with itraconazole or potassium iodide.

► MICROBIOLOGY AND IMMUNOLOGY—PARASITOLOGY

Medically important protozoa

Organism	Disease	Transmission	Diagnosis	Treatment
<i>Entamoeba histolytica</i>	Amebiasis: bloody diarrhea, (dysentery), liver abscess, RUQ pain	Cysts in water	Serology and/or trophozoites or cysts in stool	Metronidazole and iodoquinol
<i>Giardia lamblia</i> (see Color Image 5)	Giardiasis: bloating, flatulence, foul-smelling diarrhea	Cysts in water	Trophozoites or cysts in stool	Metronidazole
<i>Cryptosporidium</i>	Severe diarrhea in AIDS Mild disease (watery diarrhea) in non-HIV	Cysts in water	Cysts on acid-fast stain	None
<i>Toxoplasma</i>	Brain abscess in HIV, birth defects (ring-enhancing brain lesions)	Cysts in meat or cat feces	Serology, biopsy	Sulfadiazine + pyrimethamine
<i>Plasmodium</i> <i>P. vivax</i> <i>P. ovale</i> <i>P. malariae</i> <i>P. falciparum</i>	Malaria: cyclic fever, headache, anemia, splenomegaly Malaria—severe (cerebral) with <i>P. falciparum</i>	Mosquito (<i>Anopheles</i>)	Blood smear	Chloroquine (primaquine to prevent relapse caused by <i>P. vivax</i> , <i>P. ovale</i>), sulfadoxine + pyrimethamine, mefloquine, quinine
<i>Trichomonas vaginalis</i> (see Color Image 10)	Vaginitis: foul-smelling, greenish discharge; itching and burning	Sexual	Trophozoites on wet mount	Metronidazole
<i>Trypanosoma cruzi</i>	Chagas' disease (dilated cardiomyopathy, megacolon, megaesophagus)	Reduviid bug	Blood smear	Nifurtimox
<i>Trypanosoma</i> <i>T. gambiense</i> <i>T. rhodesiense</i>	African sleeping sickness	Tsetse fly	Blood smear	Suramin for blood-borne disease or melarsoprol for CNS penetration
<i>Leishmania donovani</i>	Visceral leishmaniasis (kala-azar)	Sandfly	Macrophages containing amastigotes	Sodium stibogluconate
<i>Babesia</i>	Babesiosis: fever and anemia	<i>Ixodes</i> tick	Blood smear, no RBC pigment, appears as "maltese cross"	Quinine, clindamycin
<i>Naegleria</i>	Rapidly fatal meningoencephalitis	Swimming in freshwater lakes (enter via cribriform plate)	Amebas in spinal fluid	None

Medically important helminths

Organism	Transmission/disease	Treatment
Cestodes (tapeworms)		
<i>Taenia solium</i>	Undercooked pork tapeworm; larvae cause mass lesions in the brain, cysticercosis.	Praziquantel/niclosamide; albendazole for cysticercosis
<i>Echinococcus granulosus</i>	Eggs in dog feces when ingested can cause cysts in liver; causes anaphylaxis if echinococcal antigens are released from cysts.	Albendazole
Trematodes (flukes)		
<i>Schistosoma</i>	Snails are host; cercariae penetrate skin of humans; causes granulomas, fibrosis, and inflammation of the spleen and liver.	Praziquantel
<i>Clonorchis sinensis</i>	Undercooked fish; causes inflammation of the biliary tract.	Praziquantel
<i>Paragonimus westermani</i>	Undercooked crab meat; causes inflammation and 2° bacterial infection of the lung.	Praziquantel
Nematodes (roundworms)		
<i>Ancylostoma duodenale</i> (hookworm)	Larvae penetrate skin of feet; intestinal infection can cause anemia.	Mebendazole/pyrantel pamoate
<i>Ascaris lumbricoides</i> (giant roundworm)	Eggs are visible in feces; intestinal infection.	Mebendazole/pyrantel pamoate
<i>Enterobius vermicularis</i> (pinworm)	Food contaminated with eggs; intestinal infection; causes anal pruritus.	Mebendazole/pyrantel pamoate
<i>Strongyloides stercoralis</i>	Larvae in soil penetrate the skin; intestinal infection.	Ivermectin/thiabendazole
<i>Trichinella spiralis</i>	Undercooked meat, usually pork; inflammation of muscle, periorbital edema.	Thiabendazole
<i>Dracunculus medinensis</i>	In drinking water; skin inflammation and ulceration.	Niridazole
<i>Loa loa</i>	Transmitted by deer fly; causes swelling in skin (can see worm crawling in conjunctiva).	Diethylcarbamazine
<i>Onchocerca volvulus</i>	Transmitted by female blackflies; causes river blindness.	Ivermectin
<i>Toxocara canis</i>	Food contaminated with eggs; causes granulomas (if in retina → blindness) and visceral larva migrans.	Diethylcarbamazine
<i>Wuchereria bancrofti</i>	Female mosquito; causes blockage of lymphatic vessels (elephantiasis).	Diethylcarbamazine

► MICROBIOLOGY AND IMMUNOLOGY—PARASITOLOGY (*continued*)

Parasite hints	Findings	Organism
	Brain cysts, seizures	<i>Taenia solium</i>
	Liver cysts	<i>Echinococcus granulosus</i>
	B ₁₂ deficiency	<i>Diphyllobothrium latum</i>
	Biliary tract disease	<i>Clonorchis sinensis</i>
	Hemoptysis	<i>Paragonimus westermani</i>
	Portal hypertension	<i>Schistosoma mansoni</i>
	Hematuria, bladder cancer	<i>Schistosoma haematobium</i>
	Microcytic anemia	<i>Ancylostoma</i> , <i>Necator</i>
	Perianal pruritus	<i>Enterobius</i>
<hr/>		
"Tricky T's"	<i>Chlamydia trachomatis</i> —bacteria, STD.	
	<i>Trichomonas vaginalis</i> —protozoan, STD.	
	<i>Trichinella spiralis</i> —worm in undercooked meat.	
	<i>Trypanosoma</i> —causes Chagas' disease (<i>T. cruzi</i>) or African sleeping sickness.	
	<i>Treponema</i> —spirochete; causes syphilis (<i>T. pallidum</i>) or yaws (<i>T. pertenue</i>).	

► MICROBIOLOGY AND IMMUNOLOGY—VIROLOGY		
DNA viral genomes	All DNA viruses except the Parvoviridae are dsDNA. All are linear except papovaviruses and hepadnaviruses (circular).	All are dsDNA (like our cells), except “ part-of-a-virus ” (parvovirus) is ssDNA.
RNA viral genomes	All RNA viruses except Reoviridae are ssRNA.	All are ssRNA (like our mRNA), except “ repeato-virus ” (reovirus) is dsRNA.
Naked viral genome infectivity	Naked nucleic acids of most dsDNA (except poxviruses and HBV) and (+) strand ssRNA (\approx mRNA) viruses are infectious. Naked nucleic acids of (–) strand ssRNA and dsRNA viruses are not infectious. Naked (nonenveloped) RNA viruses include Calicivirus, Picornavirus, and Reovirus.	Viral nucleic acids with the same structure as host nucleic acids are infective alone; others require special enzymes (contained in intact virion). Naked CPR.
Enveloped viruses	Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions are herpesviruses, which acquire envelopes from nuclear membrane.	
Virus ploidy	All viruses are haploid (with 1 copy of DNA or RNA) except retroviruses, which have 2 identical ssRNA molecules (\approx diploid).	
Viral replication		
DNA viruses	All replicate in the nucleus (except poxvirus).	
RNA viruses	All replicate in the cytoplasm (except influenza virus and retroviruses).	
DNA virus characteristics	Some general rules—all DNA viruses: 1. Are HHAPPPY viruses 2. Are double stranded 3. Are linear 4. Are icosahedral 5. Replicate in the nucleus Naked DNA viruses are PAP = Parvo, Adeno, Papova; enveloped DNA viruses are HPH = Hepadna, Pox, Herpes.	Hepadna, Herpes, Adeno, Pox, Parvo, Papova. EXCEPT Parvo (single stranded). EXCEPT Papovavirus (circular, supercoiled) and Hepadna (circular, incomplete). EXCEPT Pox (complex). EXCEPT Pox (carries own DNA-dependent RNA polymerase). You need to be naked for a PAP smear.

► MICROBIOLOGY AND IMMUNOLOGY—Virology (*continued*)**DNA viruses**

Viral Family	Envelope	DNA Structure	Medical Importance
Hepadnavirus	Yes	DS – partial circular	HBV Acute or chronic hepatitis Vaccine available—use has increased tremendously Not a retrovirus but has reverse transcriptase
Herpesviruses	Yes	DS – linear	HSV-1—oral (and some genital) lesions, keratoconjunctivitis HSV-2—genital (and some oral) lesions VZV—chickenpox, zoster, shingles EBV—mononucleosis, Burkitt's lymphoma CMV—infection in immunosuppressed patients, especially transplant recipients; congenital defects HHV-6—roseola (exanthem subitum) HHV-8—Kaposi's sarcoma—associated herpesvirus (KSHV)
Adenovirus	No	DS – linear	Febrile pharyngitis—sore throat Pneumonia Conjunctivitis—“pink eye”
Parvovirus	No	SS – linear (–) (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, “slapped cheeks” rash—erythema infectiosum (fifth disease), hydrops fetalis
Papovavirus	No	DS – circular	HPV—warts, CIN, cervical cancer JC—progressive multifocal leukoencephalopathy (PML) in HIV
Poxvirus	Yes	DS – linear (largest DNA virus)	Smallpox, although eradicated, could be used in germ warfare Vaccinia—cowpox (“milkmaid's blisters”) Molluscum contagiosum

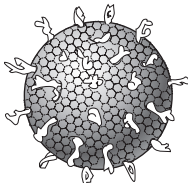
RNA viruses

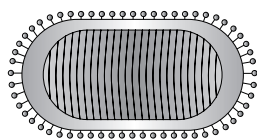
Viral Family	Envelope	RNA Structure	Capsid Symmetry	Medical Importance
Picornaviruses	No	SS + linear	Icosahedral	Poliovirus—polio-Salk/Sabin vaccines—IPV/OPV Echovirus—aseptic meningitis Rhinovirus—“common cold” Coxsackievirus—aseptic meningitis herpangina—febrile pharyngitis hand, foot, and mouth disease myocarditis HAV—acute viral hepatitis
Caliciviruses	No	SS + linear	Icosahedral	HEV Norwalk virus—viral gastroenteritis
Reoviruses	No	DS linear Segmented	Icosahedral (double)	Reovirus—Colorado tick fever Rotavirus—#1 cause of fatal diarrhea in children
Flaviviruses	Yes	SS + linear	Icosahedral	HCV Yellow fever Dengue St. Louis encephalitis West Nile virus
Togaviruses	Yes	SS + linear	Icosahedral	Rubella (German measles) Eastern equine encephalitis Western equine encephalitis
Retroviruses	Yes	SS + linear	Icosahedral	Have reverse transcriptase HIV—AIDS HTLV—T-cell leukemia
Orthomyxoviruses	Yes	SS – linear Segmented	Helical	Influenza virus
Paramyxoviruses	Yes	SS – linear Nonsegmented	Helical	PaRaMyxovirus: Parainfluenza—croup RSV—bronchiolitis in babies; Rx—ribavirin Measles Mumps
Rhabdoviruses	Yes	SS – linear	Helical	Rabies
Filoviruses	Yes	SS – linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal!
Coronaviruses	Yes	SS + linear	Helical	Coronavirus—“common cold” and SARS
Arenaviruses	Yes	SS – circular	Helical	LCV—lymphocytic choriomeningitis Meningitis—spread by mice
Bunyaviruses	Yes	SS – circular	Helical	California encephalitis Sandfly/Rift Valley fevers Crimean-Congo hemorrhagic fever Hantavirus—hemorrhagic fever, pneumonia
Deltavirus	Yes	SS – circular	Helical	HDV
SS, single-stranded; DS, double-stranded; +, + polarity; –, – polarity				

(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:182.)

► MICROBIOLOGY AND IMMUNOLOGY—VIROLOGY (*continued*)

Viral vaccines	Live attenuated vaccines induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions. Killed vaccines induce only humoral immunity but are stable.	Dangerous to give live vaccines to immunocompromised patients or their close contacts.
	Live attenuated—measles, mumps, rubella, Sabin polio, VZV, yellow fever, smallpox, adenovirus.	MMR = measles, mumps, rubella.
	Killed—rabies, influenza, HAV, and Salk polio vaccines.	SalK = Killed.
	Egg-based—Flu, MMR, Yellow fever. Recombinant—HBV (antigen = recombinant HBsAg).	FRY an egg.
<hr/>		
Viral genetics		
Recombination	Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.	
Reassortment	When viruses with segmented genomes (e.g., influenza virus) exchange segments. High-frequency recombination. Cause of worldwide pandemics.	
Complementation	When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein. The nonmutated virus “complements” the mutated one by making a functional protein that serves both viruses.	
Phenotypic mixing	Genome of virus A can be coated with the surface proteins of virus B. Type B protein coat determines the infectivity of the phenotypically mixed virus. However, the progeny from this infection has a type A coat and is encoded by its type A genetic material.	
<hr/>		
Viral pathogens		
Structure	Viruses	
DNA enveloped viruses	Herpesviruses (HSV types 1 and 2, VZV, CMV, EBV), HBV, smallpox virus	
DNA nucleocapsid viruses	Adenovirus, papillomaviruses, parvovirus	
RNA enveloped viruses	Influenza virus, parainfluenza virus, RSV, measles virus, mumps virus, rubella virus, rabies virus, HTLV, HIV	
RNA nucleocapsid viruses	Enteroviruses (poliovirus, coxsackievirus, echovirus, HAV), rhinovirus, reovirus	
<hr/>		
Slow virus infections	Virus exists in patient for months to years before it manifests as clinical disease. SSPE (late sequela of measles), PML (reactivation of JC virus) in immunocompromised patients, especially AIDS.	
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Segmented viruses	All are RNA viruses. They include B unyaviruses, O rthomyxoviruses (influenza viruses), A renaviruses, and R eoviruses. Influenza virus consists of 8 segments of negative-stranded RNA. These segments can undergo reassortment, causing antigenic shifts that lead to worldwide epidemics of the flu.	BOAR.

Picornavirus	Includes Poliovirus , Echovirus , Rhinovirus , Coxsackievirus , HAV . RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV).	PicoRNAvirus = small RNA virus. PERCH on a “ peak ” (pico).
Rhinovirus	Nonenveloped RNA virus. Cause of common cold— > 100 serologic types.	Rhino has a runny nose.
Rotavirus 	Rotavirus, the most important global cause of infantile gastroenteritis, is a segmented dsRNA virus (a reovirus). Major cause of acute diarrhea in the United States during winter.	ROTA = Right Out The Anus.
Paramyxoviruses	Paramyxoviruses include those that cause parainfluenza (croup), mumps, and measles as well as RSV, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. Paramyxoviruses cause disease in children. All paramyxoviruses have 1 serotype except parainfluenza virus, which has 4.	
Mumps virus	A paramyxovirus with 1 serotype. Symptoms: Parotitis , Orchitis (inflammation of testes), and aseptic Meningitis . Can cause sterility (especially after puberty).	Mumps makes your parotid glands and testes as big as POM -poms.
Measles virus	A paramyxovirus that causes measles. Koplik spots (bluish-gray spots on buccal mucosa) are diagnostic. SSPE, encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae.	3 C's of measles: Cough Coryza Conjunctivitis Also look for Koplik spots.
Influenza viruses	Enveloped, single-stranded RNA viruses with segmented genome. Contain hemagglutinin and neuraminidase antigens. Responsible for worldwide influenza epidemics; patients at risk for fatal bacterial superinfection. Rapid genetic changes.	Killed viral vaccine is major mode of protection; reformulated vaccine offered each fall to elderly, health-care workers, etc.
Genetic shift	Reassortment of viral genome (such as when human flu A virus recombines with swine flu A virus).	Sudden Shift is more deadly than graDual Drift .
Genetic drift	Minor changes based on random mutation.	
Treatment	Amantadine and rimantadine useful for influenza A (especially prophylaxis). Zanamivir and oseltamivir (neuraminidase inhibitors) useful for both influenza A and B.	

► MICROBIOLOGY AND IMMUNOLOGY—VIROLOGY (*continued*)**Rabies virus**

Negri bodies are characteristic cytoplasmic inclusions in neurons infected by rabies virus. Has bullet-shaped capsid. Rabies has long incubation period (weeks to 3 months). Causes fatal encephalitis with seizures and hydrophobia. More commonly from bat, raccoon, and skunk bites than from dog bites in the United States.

Travels to the CNS by migrating in a retrograde fashion up nerve axons.

Arboviruses

Transmitted by arthropods (mosquitoes, ticks). Classic examples are dengue fever (also known as break-bone fever) and yellow fever. A variant of dengue fever in Southeast Asia is hemorrhagic shock syndrome.

ARBOvirus—**AR**thropod-**BO**rne virus, including flavivirus, togavirus, and bunyavirus.

Yellow fever

Caused by flavivirus, an arbovirus transmitted by *Aedes* mosquitos. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. Councilman bodies (acidophilic inclusions) may be seen in liver.

Flavi = yellow.

Herpesviruses

Virus	Diseases	Route of transmission	
HSV-1	Gingivostomatitis, keratoconjunctivitis, temporal lobe encephalitis, herpes labialis (see Color Image 11)	Respiratory secretions, saliva	Get herpes in a CHEV olet: CMV
HSV-2	Herpes genitalis, neonatal herpes	Sexual contact, perinatal	HSV
VZV	Varicella-zoster (shingles), encephalitis, pneumonia (see Color Image 15)	Respiratory secretions	EBV
EBV	Infectious mononucleosis, Burkitt's lymphoma	Respiratory secretions, saliva	VZV
CMV	Congenital infection, mononucleosis (negative Monospot), pneumonia	Congenital, transfusion, sexual contact, saliva, urine, transplant (see Color Image 6)	
HHV-8	Kaposi's sarcoma (HIV patients)	Sexual contact	

Mononucleosis

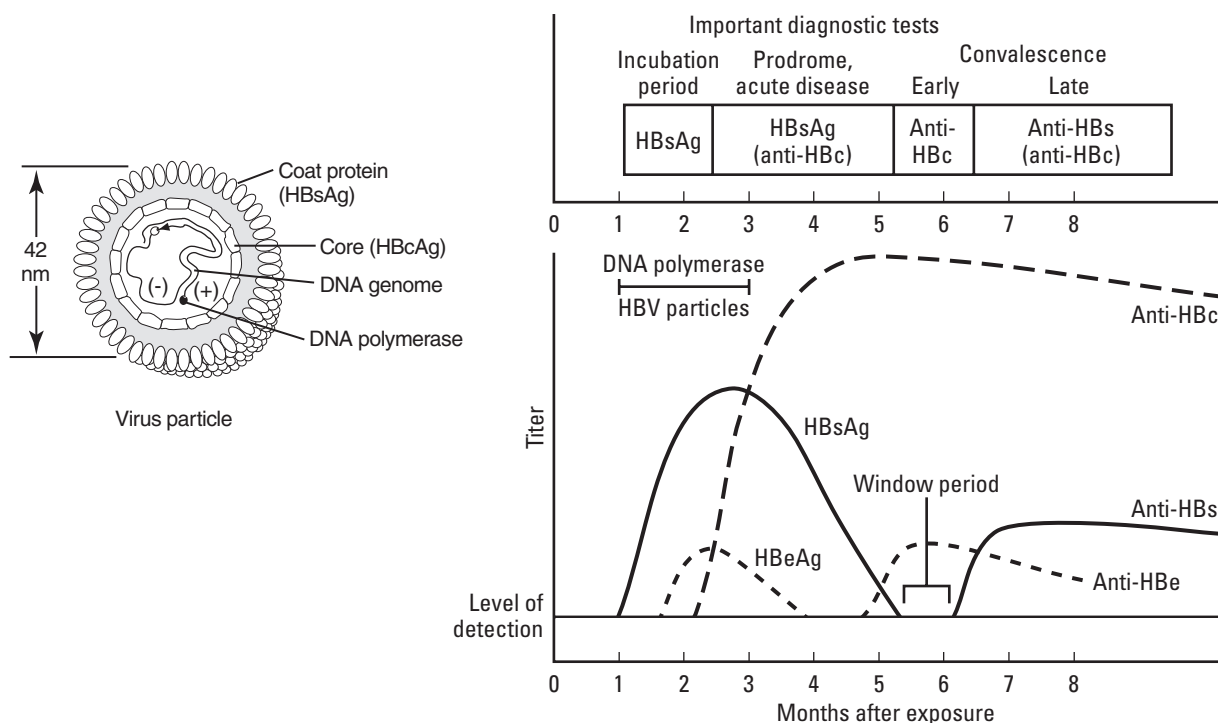
Caused by EBV, a herpesvirus. Characterized by fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior auricular nodes). Peak incidence 15–20 years old. Positive heterophil antibody test. Abnormal circulating cytotoxic T cells (atypical lymphocytes).

Most common during peak kissing years (“kissing disease”). Monospot test—heterophil antibodies detected by agglutination of sheep RBCs.

Tzanck test	A smear of an opened skin vesicle to detect multinucleated giant cells. Used to assay for HSV-1, HSV-2, and VZV.	Tzanck heavens I do not have herpes.
Hepatitis transmission	<p>HAV (RNA picornavirus) is transmitted primarily by fecal-oral route. Short incubation (3 weeks). No carriers.</p> <p>HBV (DNA hepadnavirus) is transmitted primarily by parenteral, sexual, and maternal-fetal routes. Long incubation (3 months). Carriers. Reverse transcription occurs; however, the virion enzyme is a DNA-dependent DNA polymerase.</p> <p>HCV (RNA flavivirus) is transmitted primarily via blood and resembles HBV in its course and severity. Carriers. Common cause of IV drug use hepatitis in the United States.</p> <p>HDV (delta agent) is a defective virus that requires HBsAg as its envelope. Carriers.</p> <p>HEV (RNA calicivirus) is transmitted enterically and causes water-borne epidemics. Resembles HAV in course, severity, incubation. High mortality rate in pregnant women.</p> <p>Both HBV and HCV predispose a patient to chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.</p>	<p>Hep A: Asymptomatic (usually), Acute, Alone (no carriers; naked ssRNA).</p> <p>Hep B: Blood borne.</p> <p>Hep C: Chronic, Cirrhosis, Carcinoma, Carriers.</p> <p>Hep D: Defective, Dependent on HBV.</p> <p>Hep E: Enteric, Expectant mothers, Epidemics. A and E by fecal-oral route: “The vowels hit your bowels.”</p>

► MICROBIOLOGY AND IMMUNOLOGY–VIROLOGY (*continued*)**Hepatitis serologic markers**

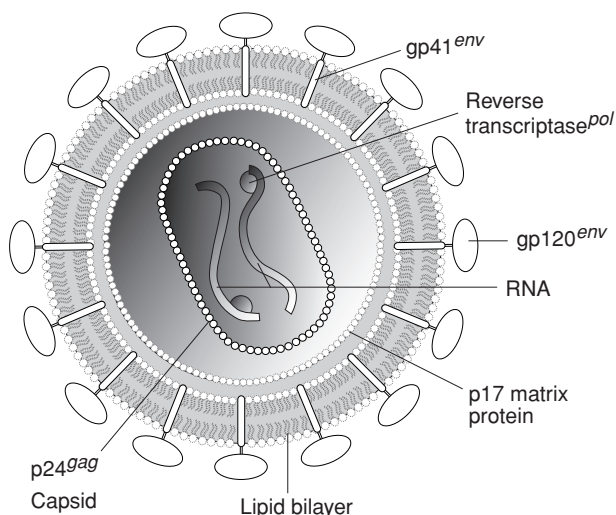
IgM HAVAb	IgM antibody to HAV; best test to detect active hepatitis A.
HBsAg	Antigen found on surface of HBV; continued presence indicates carrier state.
HBsAb	Antibody to HBsAg; provides immunity to hepatitis B.
HBcAg	Antigen associated with core of HBV.
HBcAb	Antibody to HBcAg; positive during window period . IgM HBcAb is an indicator of recent disease.
HBeAg	A second, different antigenic determinant in the HBV core. Important indicator of transmissibility. (BE ware!)
HBeAb	Antibody to e antigen; indicates low transmissibility.



Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier
HBsAg	+	–	–	+
HBsAb	–	–	+	– ^b
HBcAb	+ ^a	+	+	+

^aIgM in acute stage; IgG in chronic or recovered stage.

^bPatient has surface antibody but available antibody is bound to HBsAg.

HIV

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:314.)

Diploid genome (2 molecules of RNA).

p24 = rectangular nucleocapsid protein.

gp41 and gp120 = envelope proteins.

Reverse transcriptase synthesizes dsDNA from RNA; dsDNA integrates into host genome.

HIV diagnosis

Presumptive diagnosis made with ELISA (sensitive, high false-positive rate and low threshold, RULE OUT test); positive results are then confirmed with Western blot assay (specific, high false-negative rate and high threshold, RULE IN test).

HIV PCR/viral load tests are increasing in popularity: they allow physician to monitor the effect of drug therapy on viral load.

ELISA/Western blot tests look for antibodies to viral proteins; these tests are often falsely negative in the first 1–2 months of HIV infection and falsely positive initially in babies born to infected mothers (anti-gp120 crosses placenta).

AIDS diagnosis = < 200 CD4+, HIV positive with AIDS indicator condition (e.g., PCP), or CD4/CD8 ratio < 1.5.

HIV immunity

CCR5 mutation

Homozygous = immunity.

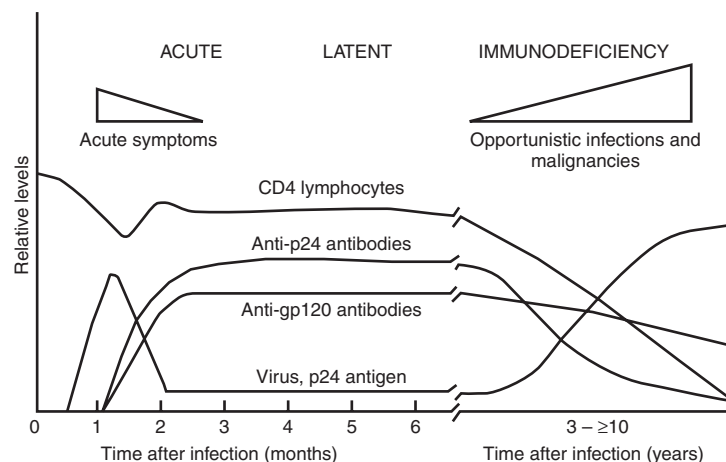
1% of U.S. Caucasians.

Heterozygous = slower course.

20% of U.S. Caucasians.

CXCR1 mutation

Rapid progression to AIDS.

► MICROBIOLOGY AND IMMUNOLOGY–VIROLOGY (*continued*)**Time course of HIV infection**

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:318.)

Opportunistic infections and disease in AIDS

Organ system	Infection/disease
Brain	Cryptococcal meningitis, toxoplasmosis, CMV encephalopathy, AIDS dementia, PML (JC virus)
Eyes	CMV retinitis
Mouth and throat	Thrush (<i>Candida albicans</i>), HSV, CMV, oral hairy leukoplakia (EBV)
Lungs	<i>Pneumocystis carinii</i> pneumonia (PCP), TB, histoplasmosis
GI	Cryptosporidiosis, <i>Mycobacterium avium–intracellulare</i> complex, CMV colitis, non-Hodgkin's lymphoma (EBV)
Skin	Shingles (VZV), Kaposi's sarcoma (HHV-8)
Genitals	Genital herpes, warts, and cervical cancer (HPV)

Prions

Infectious agents that do not contain RNA or DNA (consist only of proteins); encoded by cellular genes. Diseases include Creutzfeldt-Jakob disease (CJD—rapid progressive dementia), kuru, scrapie (sheep), and “mad cow disease.” Prions are associated with spongiform encephalopathy. Normal prions have α -helix conformation; pathologic prions (like CJD) are β -pleated sheets.

Normal flora: dominant	<p>Skin—<i>Staphylococcus epidermidis</i>. Nose—<i>S. aureus</i>. Oropharynx—viridans streptococci. Dental plaque—<i>Streptococcus mutans</i>. Colon—<i>Bacteroides fragilis</i> > <i>E. coli</i>. Vagina—<i>Lactobacillus</i>, colonized by <i>E. coli</i> and group B strep.</p>	Neonates delivered by cesarean section have no flora but are rapidly colonized after birth.
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Common causes of pneumonia	Children (6 wks–18 yr)	Adults (18–40 yr)	Adults (40–65 yr)	Elderly
	Viruses (RSV)	<i>Mycoplasma</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
	<i>Mycoplasma</i>	<i>C. pneumoniae</i>	<i>H. influenzae</i>	Viruses
	<i>Chlamydia pneumoniae</i>	<i>S. pneumoniae</i>	Anaerobes	Anaerobes
	<i>Streptococcus pneumoniae</i>		Viruses	<i>H. influenzae</i>
			<i>Mycoplasma</i>	Gram-negative rods

Special groups:

Nosocomial (hospital acquired)	<i>Staphylococcus</i> , gram-negative rods
Immunocompromised	<i>Staphylococcus</i> , gram-negative rods, fungi, viruses, <i>Pneumocystis carinii</i> —with HIV
Aspiration	Anaerobes
Alcoholic/IV drug user	<i>S. pneumoniae</i> , <i>Klebsiella</i> , <i>Staphylococcus</i>
Postviral	<i>Staphylococcus</i> , <i>H. influenzae</i>
Neonate	Group B streptococci, <i>E. coli</i>
Atypical	<i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i>

Causes of meningitis	Newborn (0–6 mos) →	Children (6 mos–6 yrs) →	6–60 yrs →	60 yrs +
Group B streptococci		<i>Streptococcus pneumoniae</i>	<i>N. meningitidis</i>	<i>S. pneumoniae</i>
<i>E. coli</i>		<i>Neisseria meningitidis</i>	Enteroviruses	Gram-negative rods
<i>Listeria</i>		<i>Haemophilus influenzae</i> type B	<i>S. pneumoniae</i>	<i>Listeria</i>
		Enteroviruses	HSV	
	In HIV— <i>Cryptococcus</i> , CMV, toxoplasmosis (brain abscess), JC virus (PML).			
	Note: Incidence of <i>H. influenzae</i> meningitis has ↓ greatly with introduction of <i>H. influenzae</i> vaccine in last 10–15 years.			

CSF findings in meningitis

	Pressure	Cell type	Protein	Sugar
Bacterial	↑	↑ PMNs	↑	↓
Fungal/TB	↑	↑ lymphocytes	↑	↓
Viral	Normal/↑	↑ lymphocytes	Normal	Normal

► MICROBIOLOGY AND IMMUNOLOGY—SYSTEMS (*continued*)

Osteomyelitis	<p>Most people—<i>S. aureus</i>.</p> <p>Sexually active—<i>Neisseria gonorrhoeae</i> (rare), septic arthritis more common.</p> <p>Diabetics and drug addicts—<i>Pseudomonas aeruginosa</i>.</p> <p>Sickle cell—<i>Salmonella</i>.</p> <p>Prosthetic replacement—<i>S. aureus</i> and <i>S. epidermidis</i>.</p> <p>Vertebral—<i>Mycobacterium tuberculosis</i> (Pott's disease).</p>	<p>Assume <i>S. aureus</i> if no other information.</p> <p>Most osteomyelitis occurs in children.</p> <p>Elevated ESR.</p>																
Urinary tract infections	<p>Ambulatory—<i>E. coli</i> (50–80%), <i>Klebsiella</i> (8–10%). <i>Staphylococcus saprophyticus</i> (10–30%) is the 2nd most common cause of UTI in young ambulatory women.</p> <p>Hospital—<i>E. coli</i>, <i>Proteus</i>, <i>Klebsiella</i>, <i>Serratia</i>, <i>Pseudomonas</i>.</p> <p>Epidemiology: women to men—10:1 (short urethra colonized by fecal flora).</p> <p>Predisposing factors: flow obstruction, kidney surgery, catheterization, gynecologic abnormalities, diabetes, and pregnancy.</p>	<p>UTIs mostly caused by ascending infections. In males: babies with congenital defects; elderly with enlarged prostates.</p> <p>UTI—dysuria, frequency, urgency, suprapubic pain.</p> <p>Pyelonephritis—fever, chills, flank pain, and CVA tenderness.</p>																
UTI bugs	<table><tr><th>Species</th><th>Features of the organism</th></tr><tr><td><i>Serratia marcescens</i></td><td>Some strains produce a red pigment; often nosocomial and drug resistant.</td></tr><tr><td><i>Staphylococcus saprophyticus</i></td><td>2nd leading cause of community-acquired UTI in sexually active women.</td></tr><tr><td><i>Escherichia coli</i></td><td>Leading cause of UTI. Colonies show metallic sheen on EMB agar.</td></tr><tr><td><i>Enterobacter cloacae</i></td><td>Often nosocomial and drug resistant.</td></tr><tr><td><i>Klebsiella pneumoniae</i></td><td>Large mucoid capsule and viscous colonies.</td></tr><tr><td><i>Proteus mirabilis</i></td><td>Motility causes “swarming” on agar; produces urease; associated with struvite stones.</td></tr><tr><td><i>Pseudomonas aeruginosa</i></td><td>Blue-green pigment and fruity odor; usually nosocomial and drug resistant.</td></tr></table>	Species	Features of the organism	<i>Serratia marcescens</i>	Some strains produce a red pigment; often nosocomial and drug resistant.	<i>Staphylococcus saprophyticus</i>	2nd leading cause of community-acquired UTI in sexually active women.	<i>Escherichia coli</i>	Leading cause of UTI. Colonies show metallic sheen on EMB agar.	<i>Enterobacter cloacae</i>	Often nosocomial and drug resistant.	<i>Klebsiella pneumoniae</i>	Large mucoid capsule and viscous colonies.	<i>Proteus mirabilis</i>	Motility causes “swarming” on agar; produces urease; associated with struvite stones.	<i>Pseudomonas aeruginosa</i>	Blue-green pigment and fruity odor; usually nosocomial and drug resistant.	<p>SSEEK PP.</p> <p>Diagnostic markers:</p> <p>Leukocyte esterase—positive = bacterial.</p> <p>Nitrite test—positive = gram negative.</p>
Species	Features of the organism																	
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Sexually transmitted diseases

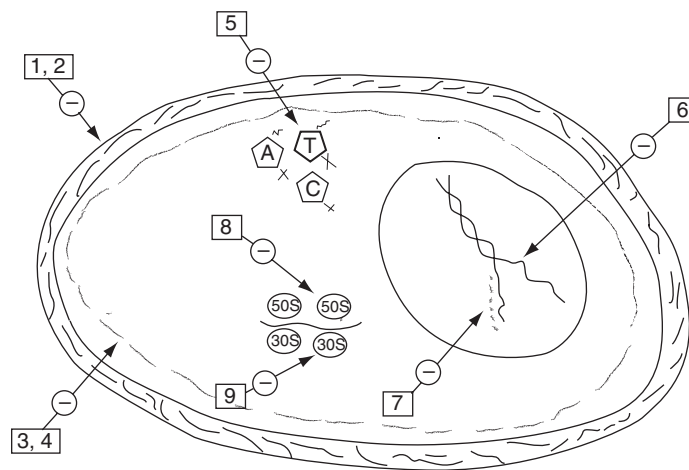
Disease	Clinical features	Organism
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	<i>Neisseria gonorrhoeae</i>
1° syphilis	Painless chancre	<i>Treponema pallidum</i>
2° syphilis	Fever, lymphadenopathy, skin rashes, condylomata lata	
3° syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Genital herpes	Painful penile, vulvar, or cervical ulcers	HSV-2
Chlamydia	Urethritis, cervicitis, conjunctivitis, Reiter's syndrome, PID	<i>Chlamydia trachomatis</i> (D–K)
Lymphogranuloma venereum	Ulcers, lymphadenopathy, rectal strictures	<i>C. trachomatis</i> (L1–L3)
Trichomoniasis	Vaginitis, strawberry-colored mucosa	<i>Trichomonas vaginalis</i>
AIDS	Opportunistic infections, Kaposi's sarcoma, lymphoma	HIV
Condylomata acuminata	Genital warts, koilocytes	HPV 6 and 11
Hepatitis B	Jaundice	HBV
Chancroid	Painful genital ulcer, inguinal adenopathy	<i>Haemophilus ducreyi</i>
Bacterial vaginosis	Noninflammatory, malodorous discharge; positive whiff test, clue cells	<i>Gardnerella vaginalis</i>
Pelvic inflammatory disease	Top bugs— <i>Chlamydia trachomatis</i> (subacute, often undiagnosed), <i>Neisseria gonorrhoeae</i> (acute, high fever). <i>C. trachomatis</i> is the most common STD in the United States (3–4 million cases per year). Cervical motion tenderness (chandelier sign), purulent cervical discharge. PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.	Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Other STDs include <i>Gardnerella</i> (clue cells) and <i>Trichomonas</i> (motile on wet prep).
Nosocomial infections		
Risk factor	Pathogen	Notes
Newborn nursery	CMV, RSV	The 2 most common causes of nosocomial infections are <i>E. coli</i> (UTI) and <i>S. aureus</i> (wound infection).
Urinary catheterization	<i>E. coli</i> , <i>Proteus mirabilis</i>	Presume <i>Pseudomonas</i> AIR uginosa when AIR or burns are involved.
Respiratory therapy equipment	<i>Pseudomonas aeruginosa</i>	
Work in renal dialysis unit	HBV	
Hyperalimentation	<i>Candida albicans</i>	
Water aerosols	<i>Legionella</i>	<i>Legionella</i> when water source is involved.
Infections dangerous in pregnancy	ToRCHeS = Toxoplasma, Rubella, CMV, HSV/HIV, Syphilis.	

► MICROBIOLOGY AND IMMUNOLOGY—SYSTEMS (*continued*)**Bug hints (if all else fails)**

Pus, empyema, abscess—*S. aureus*.
Pediatric infection—*Haemophilus influenzae* (including epiglottitis).
Pneumonia in cystic fibrosis, burn infection—*Pseudomonas aeruginosa*.
Branching rods in oral infection—*Actinomyces israelii*.
Traumatic open wound—*Clostridium perfringens*.
Surgical wound—*S. aureus*.
Dog or cat bite—*Pasteurella multocida*.
Currant jelly sputum—*Klebsiella*.
Sepsis/meningitis in newborn—group B strep.

Antimicrobial therapy

Mechanism of action	Drugs
1. Block cell wall synthesis by inhibition of peptidoglycan cross-linking	Penicillin, ampicillin, ticarcillin, piperacillin, imipenem, aztreonam, cephalosporins
2. Block peptidoglycan synthesis	Bacitracin, vancomycin, cycloserine
3. Disrupt bacterial/fungal cell membranes	Polymyxins
4. Disrupt fungal cell membranes	Amphotericin B, nystatin, fluconazole/azoles
5. Block nucleotide synthesis	Sulfonamides, trimethoprim
6. Block DNA topoisomerases	Quinolones
7. Block mRNA synthesis	Rifampin
8. Block protein synthesis at 50S ribosomal subunit	Chloramphenicol, erythromycin/macrolides, lincomycin, clindamycin, streptogramins (quinupristin, dalbapristin), linezolid
9. Block protein synthesis at 30S ribosomal subunit	Aminoglycosides, tetracyclines



Bactericidal antibiotics	Penicillin, cephalosporins, vancomycin, aminoglycosides, fluoroquinolones, metronidazole.
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► **MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS** (*continued*)

Antibiotics

[illegible]

* Required to treat *Enterobacter*.

Penicillin	Penicillin G (IV form), penicillin V (oral). Prototype β -lactam antibiotics.
Mechanism	<ol style="list-style-type: none"> 1. Bind penicillin-binding proteins 2. Block transpeptidase cross-linking of cell wall 3. Activate autolytic enzymes
Clinical use	Bactericidal for gram-positive cocci, gram-positive rods, gram-negative cocci, and spirochetes. Not penicillinase resistant.
Toxicity	Hypersensitivity reactions, hemolytic anemia.

Methicillin, nafcillin, dicloxacillin	
Mechanism	Same as penicillin. Narrow spectrum; penicillinase resistant because of bulkier R group.
Clinical use	<i>S. aureus</i> (except MRSA; resistant because of altered penicillin-binding protein target site).
Toxicity	Hypersensitivity reactions; methicillin—interstitial nephritis.

Ampicillin, amoxicillin

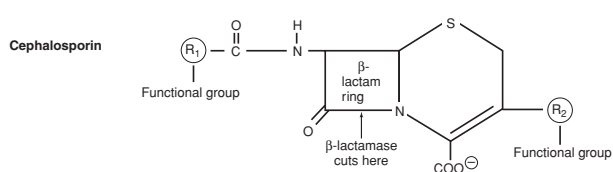
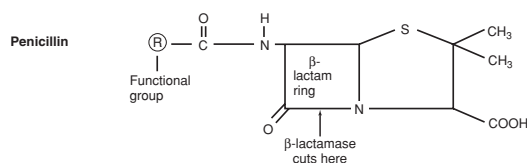
Mechanism	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid (penicillinase inhibitor) to enhance spectrum. AmOxicillin has greater Oral bioavailability than ampicillin.	
Clinical use	Extended-spectrum penicillin—certain gram-positive bacteria and gram-negative rods (<i>Haemophilus influenzae</i> , <i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , enterococci).	Coverage: ampicillin/amoxicillin HELPS kill enterococci.
Toxicity	Hypersensitivity reactions; ampicillin rash; pseudomembranous colitis.	

Ticarcillin, carbenicillin, piperacillin

Mechanism	Same as penicillin. Extended spectrum.	TCP: Takes Care of
Clinical use	<i>Pseudomonas</i> spp. and gram-negative rods; susceptible to penicillinase; use with clavulanic acid.	<i>Pseudomonas</i> .
Toxicity	Hypersensitivity reactions.	

► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)**Cephalosporins**

Mechanism	β -lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	
Clinical use	1st generation (cefazolin, cephalexin)—gram-positive cocci, <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> .	1st generation— PEcK .
	2nd generation (cefotixin, cefaclor, cefuroxime)—gram-positive cocci, <i>Haemophilus influenzae</i> , <i>Enterobacter aerogenes</i> , <i>Neisseria</i> spp., <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Serratia marcescens</i> .	2nd generation— HEN PEcKS .
	3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram-negative infections resistant to other β -lactams; meningitis (most penetrate the blood-brain barrier). Examples: ceftazidime for <i>Pseudomonas</i> ; ceftriaxone for gonorrhea.	
	4th generation (cefepime, cefpiramide)— \uparrow activity against <i>Pseudomonas</i> and gram-positive organisms.	
Toxicity	Hypersensitivity reactions. Cross-hypersensitivity with penicillins occurs in 5–10% of patients. \uparrow nephrotoxicity of aminoglycosides; disulfiram-like reaction with ethanol (in cephalosporins with a methylthiotetrazole group, e.g., cefamandole).	

**Aztreonam**

Mechanism	A monobactam resistant to β -lactamases. Inhibits cell wall synthesis (binds to PBP3). Synergistic with aminoglycosides. No cross-allergenicity with penicillins.	
Clinical use	Gram-negative rods— <i>Klebsiella</i> spp., <i>Pseudomonas</i> spp., <i>Serratia</i> spp. No activity against gram-positives or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.	
Toxicity	Usually nontoxic; occasional GI upset.	

Imipenem/cilastatin, meropenem

Mechanism	Imipenem is a broad-spectrum, β -lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dihydropeptidase I) to \downarrow inactivation in renal tubules.	With imipenem, “the kill is LASTIN ’ with ciLASTATIN .”
Clinical use	Gram-positive cocci, gram-negative rods, and anaerobes. Drug of choice for <i>Enterobacter</i> .	
Toxicity	GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.	

Vancomycin

Mechanism	Inhibits cell wall mucopeptide formation by binding D-ala D-ala portion of cell wall precursors. Bactericidal. Resistance occurs with amino acid change of D-ala D-ala to D-ala D-lac.
Clinical use	Used for serious, gram-positive multidrug-resistant organisms, including <i>S. aureus</i> and <i>Clostridium difficile</i> (pseudomembranous colitis).
Toxicity	Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing—“red man syndrome” (can largely prevent by pretreatment with antihistamines and slow infusion rate). Well tolerated in general—does NOT have many problems.

Protein synthesis inhibitors**30S inhibitors:**

“Buy AT 30, CELL at 50.”

A = Aminoglycosides (streptomycin, gentamicin, tobramycin, amikacin) [bactericidal]

T = Tetracyclines [bacteriostatic]

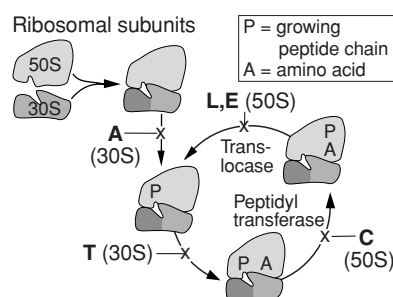
50S inhibitors:

C = Chloramphenicol [bacteriostatic]

E = Erythromycin [bacteriostatic]

L = Lincomycin [bacteriostatic]

L = cLindamycin [bacteriostatic]

**Aminoglycosides**

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.

“Mean” GNATS canNOT kill anaerobes.

Mechanism	Bactericidal; inhibit formation of initiation complex and cause misreading of mRNA. Require O ₂ for uptake; therefore ineffective against anaerobes.
Clinical use	Severe gram-negative rod infections. Synergistic with β-lactam antibiotics. Neomycin for bowel surgery.
Toxicity	Nephrotoxicity (especially when used with cephalosporins), Ototoxicity (especially when used with loop diuretics). Teratogen.

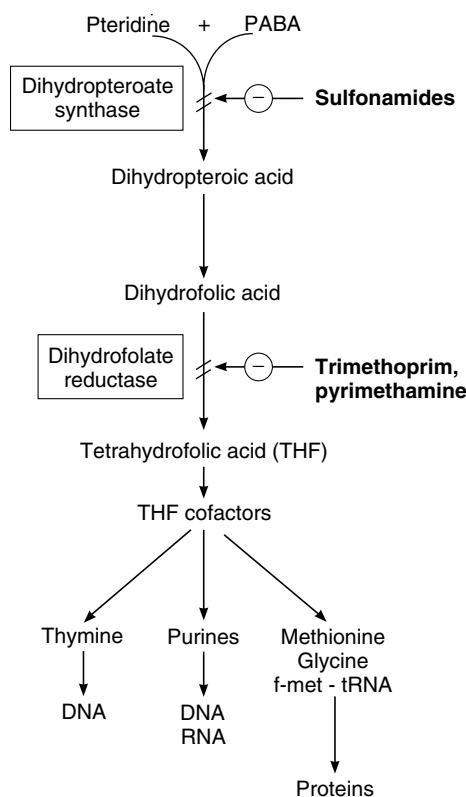
► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)

Tetracyclines		
	Tetracycline, doxycycline, demeclocycline, minocycline.	Demeclocycline—ADH antagonist; acts as a Diuretic in SIADH.
Mechanism	Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Must NOT take with milk, antacids, or iron-containing preparations because divalent cations inhibit its absorption in the gut.	
Clinical use	<i>Vibrio cholerae</i> , Acne, <i>Chlamydia</i> , <i>Ureaplasma Urealyticum</i> , <i>Mycoplasma pneumoniae</i> , Tularemia, <i>H. pylori</i> , <i>Borrelia burgdorferi</i> (Lyme disease), <i>Rickettsia</i> .	VACUUM THE BedRoom.
Toxicity	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.	
Macrolides		
Mechanism	Erythromycin, azithromycin, clarithromycin. Inhibit protein synthesis by blocking translocation; bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.	
Clinical use	URIs, pneumonias, STDs—gram-positive cocci (streptococcal infections in patients allergic to penicillin), <i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i> , <i>Neisseria</i> .	
Toxicity	GI discomfort (most common cause of noncompliance), acute cholestatic hepatitis, eosinophilia, skin rashes. Increases serum concentration of theophyllines, oral anticoagulants.	
Chloramphenicol		
Mechanism	Inhibits 50S peptidyltransferase. Bacteriostatic.	
Clinical use	Meningitis (<i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i>). Conservative use owing to toxicities.	
Toxicity	Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyl transferase).	
Clindamycin		
Mechanism	Blocks peptide bond formation at 50S ribosomal subunit. Bacteriostatic.	Treats anaerobes above the diaphragm.
Clinical use	Treat anaerobic infections (e.g., <i>Bacteroides fragilis</i> , <i>Clostridium perfringens</i>).	
Toxicity	Pseudomembranous colitis (<i>C. difficile</i> overgrowth), fever, diarrhea.	

Sulfonamides

Mechanism
Clinical use
Toxicity

Sulfamethoxazole (SMX), sulfisoxazole, triple sulfas, sulfadiazine.
PABA antimetabolites inhibit dihydropteroate synthase. Bacteriostatic.
Gram-positive, gram-negative, *Nocardia*, *Chlamydia*. Triple sulfas or SMX for simple UTI.
Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), kernicterus in infants, displace other drugs from albumin (e.g., warfarin).



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:762.)

Trimethoprim

Mechanism
Clinical use

Inhibits bacterial dihydrofolate reductase. Bacteriostatic.
Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis.
Combination used for recurrent UTIs, *Shigella*, *Salmonella*, *Pneumocystis carinii* pneumonia.
Megaloblastic anemia, leukopenia, granulocytopenia.
(May alleviate with supplemental folinic acid.)

Trimethoprim = TMP:
“Treats Marrow Poorly.”

Toxicity

► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)

Fluoroquinolones		
	Ciprofloxacin, norfloxacin, ofloxacin, sparfloxacin, moxifloxacin, gatifloxacin, enoxacin (fluoroquinolones), nalidixic acid (a quinolone).	
Mechanism	Inhibit DNA gyrase (topoisomerase II). Bactericidal.	Fluoroquinolones hurt
Clinical use	Gram-negative rods of urinary and GI tracts (including <i>Pseudomonas</i>), <i>Neisseria</i> , some gram-positive organisms.	attachments to your
		BONES.
Toxicity	GI upset, superinfections, skin rashes, headache, dizziness. Contraindicated in pregnant women and in children because animal studies show damage to cartilage. Tendonitis and tendon rupture in adults; leg cramps and myalgias in kids.	
Metronidazole		
Mechanism	Forms toxic metabolites in the bacterial cell. Bactericidal.	
Clinical use	Antiprotozoal. <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , anaerobes (<i>Bacteroides</i> , <i>Clostridium</i>). Used with bismuth and amoxicillin (or tetracycline) for “triple therapy” against <i>H. pylori</i> .	GET on the Metro!
		Anaerobic infection below the diaphragm.
Toxicity	Disulfiram-like reaction with alcohol; headache, metallic taste.	
Polymyxins		
	Polymyxin B, polymyxin E.	’MYXins MIX up membranes.
Mechanism	Bind to cell membranes of bacteria and disrupt their osmotic properties. Polymyxins are cationic, basic proteins that act like detergents.	
Clinical use	Resistant gram-negative infections.	
Toxicity	Neurotoxicity, acute renal tubular necrosis.	
Anti-TB drugs		
	Streptomycin, Pyrazinamide, Isoniazid (INH), Rifampin, Ethambutol.	INH-SPIRE (inspire).
	Cycloserine (2nd-line therapy).	Isoniazid (INH) used alone for TB prophylaxis; all used in combination for TB treatment.
		All are hepatotoxic.
Isoniazid (INH)		
Mechanism	↓ synthesis of mycolic acids.	INH Injures Neurons and
Clinical use	<i>Mycobacterium tuberculosis</i> . The only agent used as solo prophylaxis against TB.	Hepatocytes.
		Different INH half-lives in fast
Toxicity	Hemolysis if G6PD deficient, neurotoxicity, hepatotoxicity, SLE-like syndrome. Pyridoxine (vitamin B ₆) can prevent neurotoxicity.	vs. slow acetylators.

Rifampin

Mechanism	Inhibits DNA-dependent RNA polymerase.
Clinical use	<i>Mycobacterium tuberculosis</i> ; delays resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with <i>Haemophilus influenzae</i> type B.
Toxicity	Minor hepatotoxicity and drug interactions (↑ P-450).

Rifampin's 4 R's:

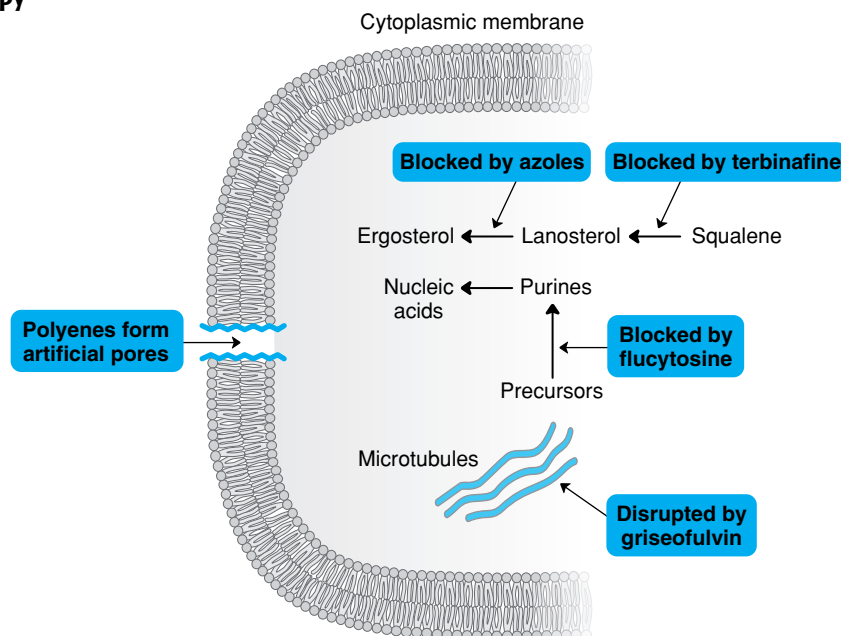
RNA polymerase inhibitor
 Revs up microsomal P-450
 Red/orange body fluids
 Rapid resistance if used alone

Resistance mechanisms for various antibiotics

Drug	Most common mechanism
Penicillins/ cephalosporins	β-lactamase cleavage of β-lactam ring
Aminoglycosides	Modification via acetylation, adenylation, or phosphorylation
Vancomycin	Terminal D-ala of cell wall component replaced with D-lac; ↓ affinity.
Chloramphenicol	Modification via acetylation
Macrolides	Methylation of rRNA near erythromycin's ribosome-binding site
Tetracycline	↓ uptake or ↑ transport out of cell
Sulfonamides	Altered enzyme (bacterial dihydropteroate synthetase), ↓ uptake, or ↑ PABA synthesis

Nonsurgical antimicrobial prophylaxis

Meningococcal infection	Rifampin (drug of choice), minocycline.
Gonorrhea	Ceftriaxone.
Syphilis	Benzathine penicillin G.
History of recurrent UTIs	TMP-SMX.
<i>Pneumocystis carinii</i> pneumonia	TMP-SMX (drug of choice), aerosolized pentamidine.
Endocarditis with surgical or dental procedures	Penicillins.

► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)**Antifungal therapy**

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:120.)

Amphotericin B

Mechanism	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes and disrupt homeostasis.	Amphotericin “tears” holes in the fungal membrane by forming pores.
Clinical use	Used for wide spectrum of systemic mycoses. <i>Cryptococcus</i> , <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Aspergillus</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> (systemic mycoses). Intrathecally for fungal meningitis; does not cross blood-brain barrier.	
Toxicity	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias (“amphoterrible”).	

Nystatin

Mechanism	Binds to ergosterol, disrupting fungal membranes. Too toxic for systemic use.
Clinical use	“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

Fluconazole, ketoconazole, clotrimazole, miconazole, itraconazole, voriconazole

Mechanism	Inhibit fungal steroid (ergosterol) synthesis.
Clinical use	Systemic mycoses. Fluconazole for cryptococcal meningitis in AIDS patients and candidal infections of all types (i.e., yeast infections). Ketoconazole for <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Candida albicans</i> ; hypercortisolism.
Toxicity	Hormone synthesis inhibition (gynecomastia), liver dysfunction (inhibits cytochrome P-450), fever, chills.

Flucytosine

Mechanism	Inhibits DNA synthesis by conversion to fluorouracil, which competes with uracil.
Clinical use	Used in systemic fungal infections (e.g., <i>Candida</i> , <i>Cryptococcus</i>).
Toxicity	Nausea, vomiting, diarrhea, bone marrow suppression.

Caspofungin

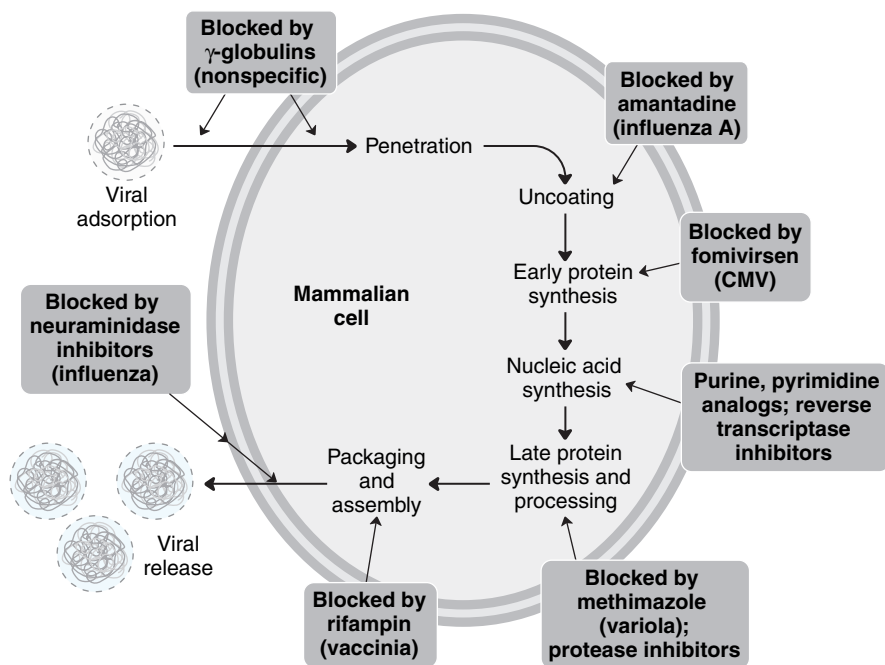
Mechanism	Inhibits cell wall synthesis.
Clinical use	Invasive aspergillosis.
Toxicity	GI upset, flushing.

Terbinafine

Mechanism	Inhibits the fungal enzyme squalene epoxidase.
Clinical use	Used to treat dermatophytoses (especially onychomycosis).

Griseofulvin

Mechanism	Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (e.g., nails).
Clinical use	Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).
Toxicity	Teratogenic, carcinogenic, confusion, headaches, ↑ warfarin metabolism.

Antiviral chemotherapy

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:120.)

► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)**Amantadine**

Mechanism	Blocks viral penetration/uncoating; may buffer pH of endosome. Also causes the release of dopamine from intact nerve terminals.	“A man to dine” takes off his coat.
Clinical use	Prophylaxis and treatment for influenza A; Parkinson’s disease.	Amantadine blocks influenza A and rubella and causes problems with the cerebellum.
Toxicity	Ataxia, dizziness, slurred speech.	Rimantidine is a derivative with fewer CNS side effects.

Zanamivir, oseltamivir

Mechanism	Inhibit influenza neuraminidase.
Clinical use	Both influenza A and B.

Ribavirin

Mechanism	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase.
Clinical use	RSV, chronic hepatitis C.
Toxicity	Hemolytic anemia. Severe teratogen.

Acyclovir

Mechanism	Preferentially inhibits viral DNA polymerase when phosphorylated by viral thymidine kinase.
Clinical use	HSV, VZV, EBV. Mucocutaneous and genital herpes lesions. Prophylaxis in immunocompromised patients.
Toxicity	Delirium, tremor, nephrotoxicity.

Ganciclovir

Mechanism	Phosphorylation by viral kinase; preferentially inhibits CMV DNA polymerase.
Clinical use	CMV, especially in immunocompromised patients.
Toxicity	Leukopenia, neutropenia, thrombocytopenia, renal toxicity. More toxic to host enzymes than acyclovir.

Foscarnet

Mechanism	Viral DNA polymerase inhibitor that binds to the pyrophosphate binding site of the enzyme. Does not require activation by viral kinase.	FOScarnet = pyroFOSphate analog.
Clinical use	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.	
Toxicity	Nephrotoxicity.	

HIV therapy

Protease inhibitors	Saquinavir, ritonavir, indinavir, nelfinavir, amprenavir.	Never (navir) tease a pro—protease inhibitors.
Mechanism	Inhibit assembly of new virus by blocking protease enzyme.	
Toxicity	GI intolerance (nausea, diarrhea), hyperglycemia, lipid abnormalities, thrombocytopenia (indinavir).	

Reverse transcriptase inhibitors

Nucleosides	Zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir.
Non-nucleosides	Nevirapine, delavirdine, efavirenz.
Mechanism	Preferentially inhibit reverse transcriptase of HIV; prevent incorporation of viral genome into host DNA.
Toxicity	Bone marrow suppression (neutropenia, anemia), peripheral neuropathy, lactic acidosis (nucleosides), rash (non-nucleosides), megaloblastic anemia (AZT).
Clinical use	Highly active antiretroviral therapy (HAART) generally entails combination therapy with protease inhibitors and reverse transcriptase inhibitors. Initiated when patients have low CD4 counts (< 500 cells/mm ³) or high viral load. AZT is used during pregnancy to reduce risk of fetal transmission.

Interferons

Mechanism	Glycoproteins from human leukocytes that block various stages of viral RNA and DNA synthesis.
Clinical use	IFN- α —chronic hepatitis B and C, Kaposi's sarcoma. IFN- β —MS. IFN- γ —NADPH oxidase deficiency.
Toxicity	Neutropenia.

► MICROBIOLOGY AND IMMUNOLOGY—ANTIMICROBIALS (*continued*)**Antiparasitic drugs**

Ivermectin	Onchocerciasis (rIVER blindness treated with IVERmectin).
Mebendazole/ thiabendazole	Nematode/roundworm (e.g., pinworm, whipworm) infections.
Pyrantel pamoate	Giant roundworm (<i>Ascaris</i>), hookworm (<i>Necator/Ancylostoma</i>), pinworm (<i>Enterobius</i>).
Praziquantel	Trematode/fluke (e.g., schistosomes, <i>Paragonimus</i> , <i>Clonorchis</i>) and cysticercosis.
Niclosamide	Cestode/tapeworm (e.g., <i>Diphyllobothrium latum</i> , <i>Taenia</i> species) infections except cysticercosis.
Pentavalent antimony	Leishmaniasis.
Chloroquine, quinine, mefloquine, atovaquone, proguanil	Malaria.
Primaquine	Latent hypnozoite (liver) forms of malaria (<i>Plasmodium vivax</i> , <i>P. ovale</i>).
Metronidazole	Giardiasis, amebic dysentery (<i>Entamoeba histolytica</i>), bacterial vaginitis (<i>Gardnerella vaginalis</i>), <i>Trichomonas</i> .
TMP-SMX, pentamidine	<i>Pneumocystis carinii</i> pneumonia prophylaxis.
Nifurtimox	Chagas' disease, American trypanosomiasis (<i>Trypanosoma cruzi</i>).
Suramin	African trypanosomiasis (sleeping sickness).

**Antibiotics to avoid
in pregnancy**

Sulfonamides—kernicterus.
 Aminoglycosides—ototoxicity.
 Fluoroquinolones—cartilage damage.
 Erythromycin—acute cholestatic hepatitis in mom
 (and clarithromycin—embryotoxic).
 Metronidazole—mutagenesis.
 Tetracyclines—discolored teeth, inhibition of bone
 growth.
 Ribavirin (antiviral)—teratogenic.
 Griseofulvin (antifungal)—teratogenic.
 Chloramphenicol—"gray baby."

**SAFE Moms Take Really
Good Care.**

Lymph node

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage/proliferation of B and T cells, antibody production.

Follicle

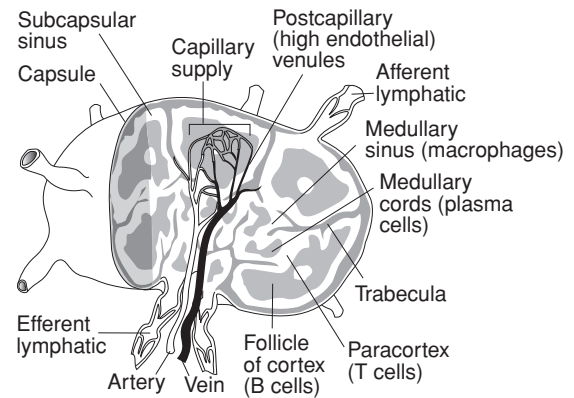
Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and dormant. 2° follicles have pale central germinal centers and are active.

Medulla

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

Paracortex

Houses T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. In an extreme cellular immune response, paracortex becomes greatly enlarged. Not well developed in patients with DiGeorge syndrome.



Paracortex enlarges in an extreme cellular immune response (i.e., viral).

Lymph drainage

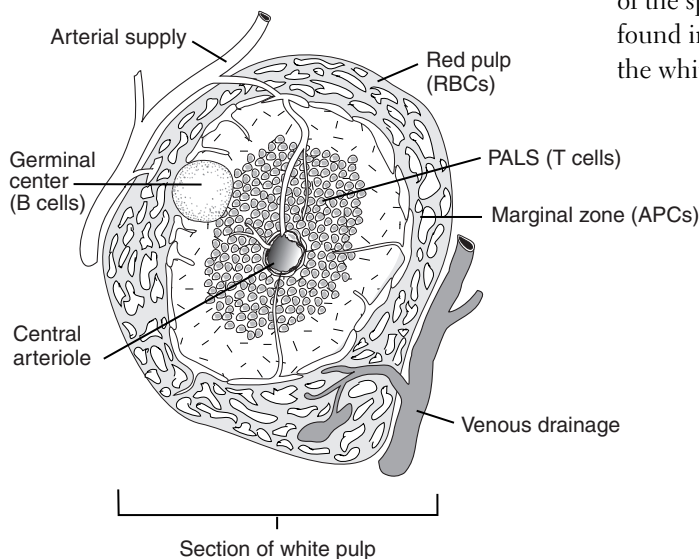
Right lymphatic duct	Drains right arm and right half of head.
Thoracic duct	Drains everything else.

► MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)

Sinusoids of spleen

Long, vascular channels in red pulp with fenestrated “barrel hoop” basement membrane. Macrophages found nearby.

T cells are found in the periarterial lymphatic sheath (PALS) and in the red pulp of the spleen. B cells are found in follicles within the white pulp of the spleen.



(Adapted, with permission, from Janeway CA, Travers P, Walport M, Capra JD. *Immunobiology: The Immune System in Health and Disease*, 4th ed. New York: Garland, 1999.)

Thymus

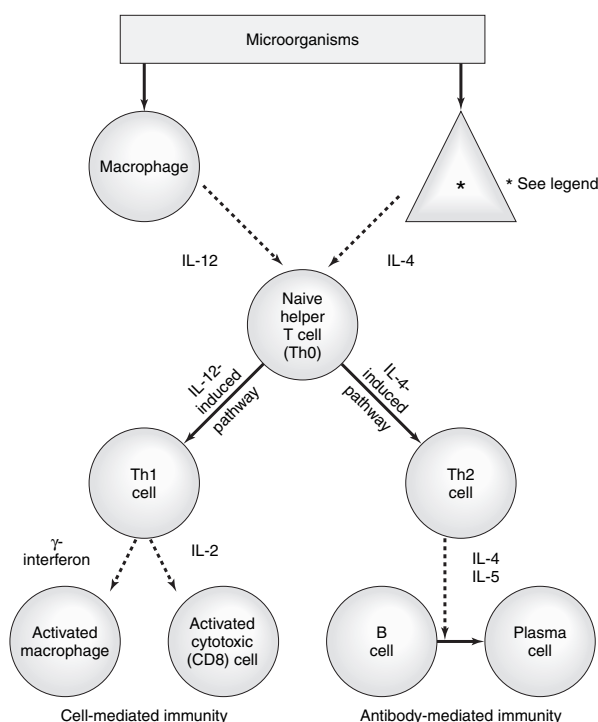
Site of T-cell maturation. Encapsulated. From epithelium of 3rd branchial pouches. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and epithelial reticular cells and contains Hassall's corpuscles. Positive selection (MHC restriction) and negative selection (nonreactive to self) occur at the corticomedullary junction.

Think of the Thymus as “finishing school” for T cells. They arrive immature and “dense” in the cortex; they are mature in the medulla.

Differentiation of B and T cells

Th1 cells (produce IL-2 and γ -interferon)—activate macrophages (increase killing efficiency of intracellular bacteria) and Tc cells.

Th2 cells (produce IL-4 and IL-5)—help B cells make antibody (B = 2nd letter of alphabet).



*The human cell that produces the IL-4 that induces naive helper T cells to become Th2 cells has not been identified.

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:398.)

Major function of B cells and T cells

Antibody-mediated immunity (B cells)

Host defense against infection (opsonize bacteria, neutralize toxins and viruses)

Allergy (e.g., hay fever, type I hypersensitivity)

Autoimmunity

Cell-mediated immunity (T cells)

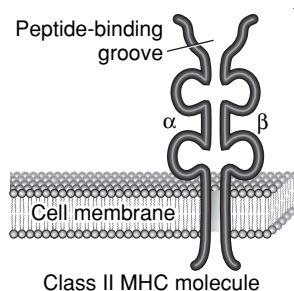
Host defense against infection (especially *Mycobacterium tuberculosis*, virus-infected cells, and fungi)

Allergy (e.g., poison oak, type IV hypersensitivity)

Graft and tumor rejection

Regulation of antibody response (help and suppression)

(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:337.)

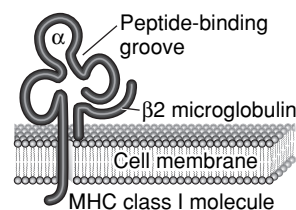
► MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)**MHC I and II**

MHC—major histocompatibility complex. Consists of 3 class I genes (A, B, C) and 3 class II genes (DP, DQ, DR). All nucleated cells have MHC I proteins.

Antigen-presenting cells (e.g., macrophages and dendritic cells) have MHC II and MHC I proteins. Class II are the main determinants of organ rejection. MHC I antigen loading occurs in RER (viral antigens). MHC II antigen loading occurs in acidified endosome.

Class I—1 polypeptide, with β_2 -microglobulin.

Class II—2 polypeptides, an α and a β chain.

**T-cell glycoproteins**

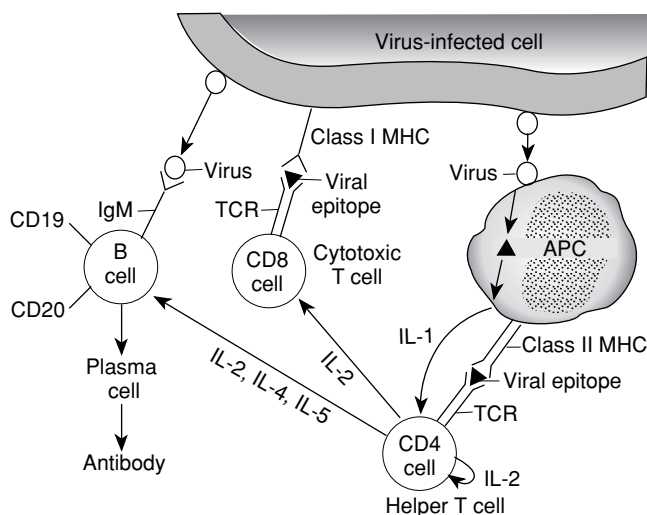
Helper T cells have CD4, which binds to MHC II on antigen-presenting cells. Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

Product of CD and MHC = 8
($CD4 \times MHC II = 8 = CD8 \times MHC I$).

CD3 complex—cluster of polypeptides associated with a T-cell receptor. Important in signal transduction.

Antigen-presenting cells:

1. Macrophage
2. B cell
3. Dendritic cell



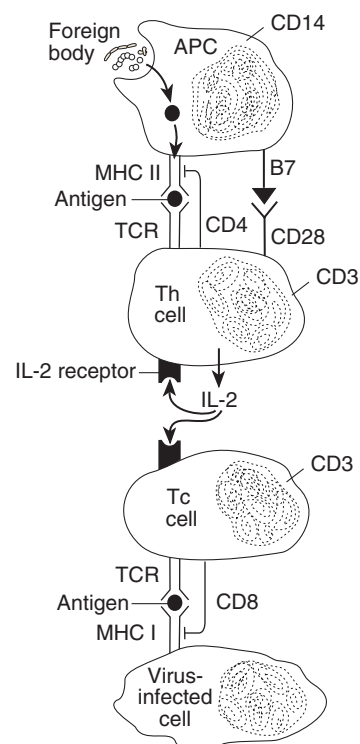
T-cell activation

Th activation:

1. Foreign body is phagocytosed by APC
2. Foreign antigen is presented on MHC II and recognized by TCR on Th cell
3. “Costimulatory signal” is given by interaction of B7 and CD28
4. Th cell activated to produce IL-2 and γ -interferon

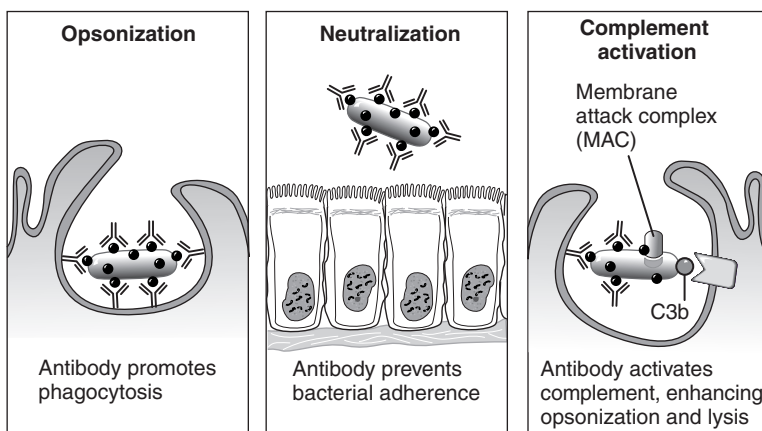
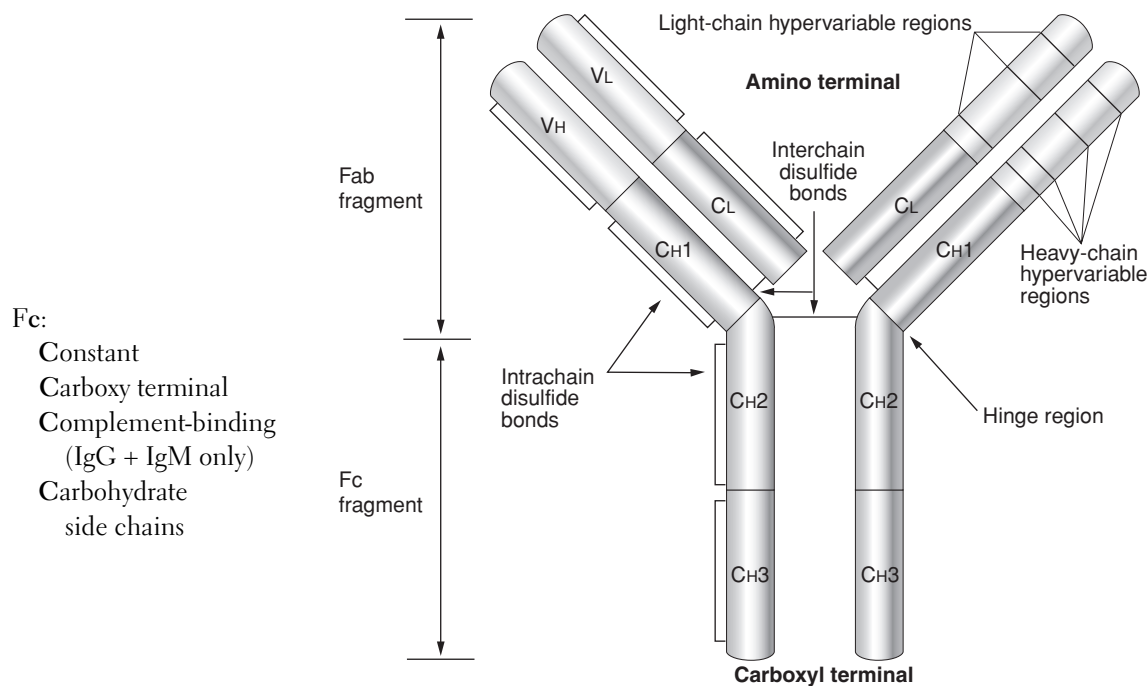
Tc activation:

1. Endogenously synthesized (viral or self) proteins are presented on MHC I and recognized by TCR on Tc cell
2. IL-2 from Th cell activates Tc cell to kill virus-infected cell



► MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)**Antibody structure and function**

Variable part of L and H chains recognizes antigens. Constant part of H chain of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab fractions. Light chain contributes only to Fab fraction.



Antibody diversity is generated by:

1. Random "recombination" of VJ (light-chain) or VDJ (heavy-chain) genes
2. Random combination of heavy chains with light chains
3. Somatic hypermutation
4. Addition of nucleotides to DNA during "genetic recombination" by terminal deoxynucleotidyl transferase

Immunoglobulin isotypes	<p>Mature B lymphocytes express IgM and IgD on their surfaces. They may differentiate by isotype switching (mediated by cytokines and CD40 ligand) into plasma cells that secrete IgA, IgE, or IgG.</p> <p>IgG: Main antibody in 2° response. Most abundant. Fixes complement, crosses the placenta, opsonizes bacteria, neutralizes bacterial toxins and viruses.</p> <p>IgA: Prevents attachment of bacteria and viruses to mucous membranes, does not fix complement. Monomer or dimer. Found in secretions. Picks up secretory component from epithelial cells before secretion.</p> <p>IgM: Produced in the 1° response to an antigen. Fixes complement but does not cross the placenta. Antigen receptor on the surface of B cells. Monomer or pentamer.</p> <p>IgD: Unclear function. Found on the surface of many B cells and in serum.</p> <p>IgE: Mediates immediate (type I) hypersensitivity by inducing the release of mediators from mast cells and basophils when exposed to allergen. Mediates immunity to worms. Lowest concentration in serum.</p>	
Ig epitopes	<p>Allotype (polymorphism)—Ig epitope that differs among members of same species. Can be on light chain or heavy chain.</p> <p>Isotype (IgG, IgA, etc.)—Ig epitope common to a single class of Ig (5 classes, determined by heavy chain).</p> <p>Idiotypic (specific for a given antigen)—Ig epitope determined by antigen-binding site.</p>	<p>Isotype = <i>iso</i> (same). Common to same class.</p> <p>Idiotypic = <i>idio</i> (unique). Hypervariable region is unique.</p>

► MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)**Important cytokines**

IL-1	Secreted by macrophages. Stimulates T cells, B cells, neutrophils, fibroblasts, and epithelial cells to grow, differentiate, or synthesize specific products. An endogenous pyrogen.	“Hot T-bone stEak”: IL-1: fever (hot) IL-2: stimulates T cells IL-3: stimulates bone marrow IL-4: stimulates IgE production IL-5: stimulates IgA production
IL-2	Secreted by Th cells. Stimulates growth of helper and cytotoxic T cells.	
IL-3	Secreted by activated T cells. Supports the growth and differentiation of bone marrow stem cells. Has a function similar to GM-CSF.	
IL-4	Secreted by Th cells. Promotes growth of B cells. Enhances class switching of IgE and IgG.	
IL-5	Secreted by Th cells. Promotes differentiation of B cells. Enhances class switching of IgA. Stimulates production and activation of eosinophils.	
IL-6	Secreted by Th cells and macrophages. Stimulates production of acute-phase reactants and immunoglobulins.	
IL-8	Major chemotactic factor for neutrophils.	
IL-10	Secreted by Th2 cells. Stimulates Th2 while inhibiting Th1.	
IL-12	Secreted by B cells and macrophages. Activates NK and Th1 cells.	
γ -interferon	Secreted by Th cells. Stimulates macrophages.	
TNF- α	Secreted by macrophages. \uparrow IL-2 receptor synthesis by Th cells. \uparrow B-cell proliferation. Attracts and activates neutrophils. Stimulates dendritic cell migration to lymph nodes.	

Cell surface proteins

Helper T cells	CD4, TCR, CD3, CD28, CD40L.
Cytotoxic T cells	CD8, TCR, CD3.
B cells	IgM, B7, CD19, CD20, CD40, MHC II.
Macrophages	MHC II, CD14. Receptors for Fc and C3b.
NK cells	Receptors for MHC I, CD16.
All cells except mature red cells	MHC I.

Complement

System of proteins that interact to play a role in humoral immunity and inflammation.

Complement defends against gram-negative bacteria.

Activated by IgG or IgM in the **classic** pathway, and activated by molecules on the surface of microbes (especially endotoxin) in the **alternate** pathway.

GM makes **classic** cars.

C1, C2, C3, C4—viral neutralization.

C3b—opsonization.

C3a, C5a—anaphylaxis.

C5a—neutrophil chemotaxis.

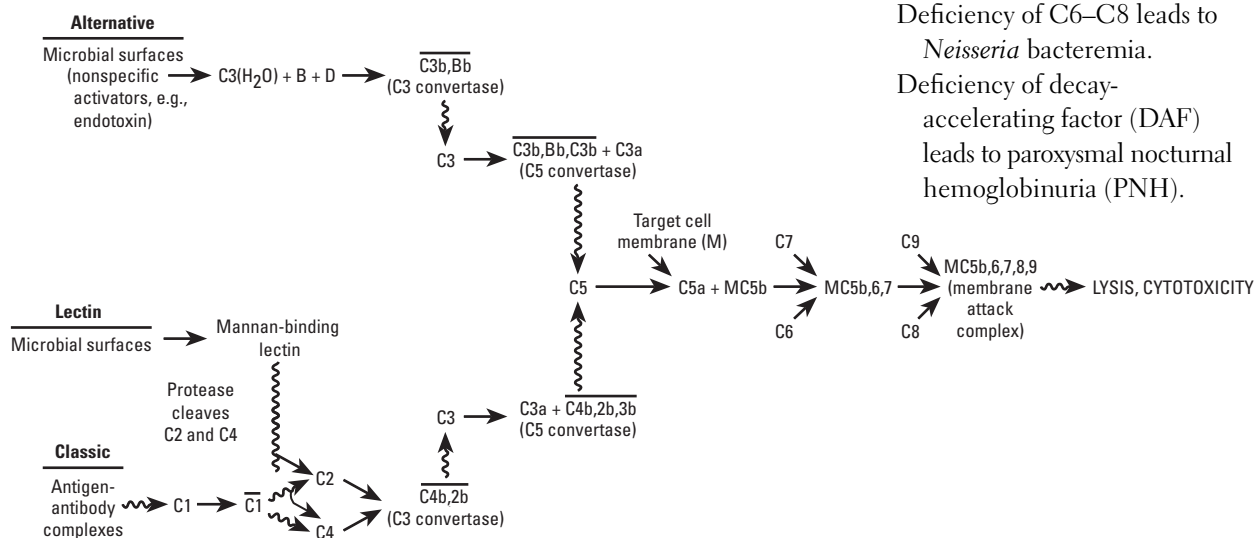
C5b-9—cytolysis by membrane attack complex (MAC).

Deficiency of C1 esterase inhibitor leads to hereditary angioedema (overactive complement).

Deficiency of C3 leads to severe, recurrent pyogenic sinus and respiratory tract infections.

Deficiency of C6–C8 leads to *Neisseria* bacteremia.

Deficiency of decay-accelerating factor (DAF) leads to paroxysmal nocturnal hemoglobinuria (PNH).



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:432.)

Interferon mechanism

Interferons (α , β , γ) are proteins that place uninfected cells in an antiviral state. Interferons induce the production of a 2nd protein that inhibits viral protein synthesis by degrading viral mRNA (but not host mRNA).

Interferes with viral protein synthesis by:

1. α - and β -interferons inhibit viral protein synthesis
2. γ -interferons \uparrow MHC I and II expression and antigen presentation in all cells
3. Activates NK cells to kill virus-infected cells

► MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)**Passive vs. active immunity**

Active	Induced after exposure to foreign antigens. Slow onset. Long-lasting protection (memory).	After exposure to Tetanus toxin, Botulinum toxin, HBV, or Rabies, patients are given preformed antibodies (passive)— To Be Healed Rapidly.
Passive	Based on receiving preformed antibodies from another host. Rapid onset. Short life span of antibodies.	

Antigen variation

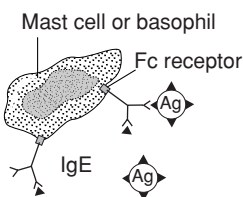
Classic examples: Bacteria— <i>Salmonella</i> (two flagellar variants), <i>Borrelia</i> (relapsing fever), <i>Neisseria gonorrhoeae</i> (pilus protein). Virus—influenza (major = shift, minor = drift). Parasites—trypanosomes (programmed rearrangement).	Some mechanisms for variation include DNA rearrangement and RNA segment rearrangement (e.g., influenza major shift).
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Anergy

Self-reactive T cells become nonreactive without costimulatory molecule. B cells also become anergic, but tolerance is less complete than in T cells.
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Hypersensitivity

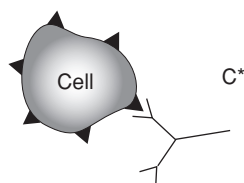
Type I



Anaphylactic and atopic—antigen cross-links IgE on presensitized mast cells and basophils, triggering release of vasoactive amines (i.e., histamine). Reaction develops rapidly after antigen exposure due to preformed antibody. Examples include anaphylaxis, asthma, hives, local wheal and flare.

First and Fast (anaphylaxis).
Types I, II, and III are all antibody mediated.

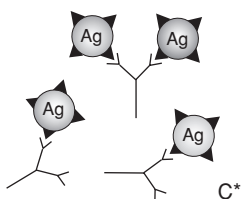
Type II



Antibody mediated—IgM, IgG bind to antigen on “enemy” cell, leading to lysis (by complement) or phagocytosis. Examples include autoimmune hemolytic anemia, Rh disease (erythroblastosis fetalis), Goodpasture’s syndrome, rheumatic fever, Graves’ disease, bullous pemphigoid, myasthenia gravis, ITP.

Cy-2-toxic.
Antibody and complement lead to membrane attack complex (MAC).

Type III



Immune complex—antigen-antibody complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes. Examples include PAN, immune complex glomerulonephritis, SLE, rheumatoid arthritis.

Imagine an immune complex as **3 things stuck together:**
antigen-antibody-complement.

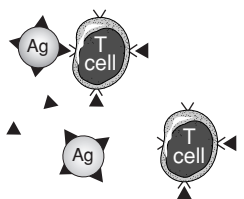
Serum sickness—an immune complex disease (type III) in which antibodies to the foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Most serum sickness is now caused by drugs (not serum).
Fever, urticaria, arthralgias, proteinuria, lymphadenopathy 5–10 days after antigen exposure.

Arthus reaction—a local subacute antibody-mediated hypersensitivity (type III) reaction. Intradermal injection of antigen induces antibodies, which form antigen-antibody complexes in the skin. Characterized by edema, necrosis, and activation of complement. Examples include hypersensitivity pneumonitis (farmer’s lung), thermophilic actinomycetes.

Antigen-antibody complexes cause the Arthus reaction.

Type IV



Delayed (T-cell-mediated) type—sensitized T lymphocytes encounter antigen and then release lymphokines (leads to macrophage activation).

4th and last—delayed. Cell mediated; therefore, it is not transferable by serum.

4 T’s = T lymphocytes,
Transplant rejections,
TB skin tests, Touching (contact dermatitis).

ACID:

Anaphylactic and Atopic (type I)

Cytotoxic (antibody mediated) (type II)

Immune complex (type III)

Delayed (cell mediated) (type IV)

C* = complement

▶ MICROBIOLOGY AND IMMUNOLOGY—IMMUNOLOGY (*continued*)**Immune deficiencies****1. ↓ production of:**

B cells—Bruton's
agammaglob-
ulinemia

X-linked recessive defect in a tyrosine kinase gene associated with low levels of all classes of immunoglobulins. Associated with recurrent **Bacterial** infections after 6 months of age, when levels of maternal IgG antibody decline. Occurs in **Boys** (X-linked).

T cells—Thymic aplasia
(DiGeorge
syndrome)

Thymus and parathyroids fail to develop owing to failure of development of the 3rd and 4th pharyngeal pouches. Presents with **Tetany** owing to hypocalcemia. Recurrent viral and fungal infections due to T-cell deficiency. Congenital defects of heart and great vessels. 22q11 deletion.

B and T cells—
severe combined
immunodeficiency
(SCID)

Defect in early stem-cell differentiation. Presents with recurrent viral, bacterial, fungal, and protozoal infections. May have multiple causes (e.g., failure to synthesize MHC II antigens, defective IL-2 receptors, or adenosine deaminase deficiency).

2. ↓ activation of:

T cells—IL-12
receptor deficiency

Presents with disseminated mycobacterial infections.

B cells—hyper-
IgM syndrome

Defect in CD40 ligand on CD4 T helper cells leads to inability to class switch. Presents early in life with severe pyogenic infections. High levels of IgM; very low levels of IgG, IgA, and IgE.

B cells—
Wiskott-Aldrich
syndrome

X-linked defect in the ability to mount an IgM response to capsular polysaccharides of bacteria. Associated with elevated IgA levels, normal IgE levels, and low IgM levels. Triad of symptoms includes recurrent pyogenic **Infections**, thrombocytopenic **Purpura**, **Eczema** (**WIPE**).

Macrophages—
Job's syndrome

Failure of γ -interferon production by helper T cells. Neutrophils fail to respond to chemotactic stimuli. Presents with recurrent "cold" (noninflamed) staphylococcal abscesses, eczema, coarse facies, retained primary teeth, and high levels of IgE.

3. Phagocytic cell deficiency:

Leukocyte adhesion
deficiency syndrome

Defect in LFA-1 adhesion proteins on phagocytes. Presents early with severe pyogenic and fungal infections and delayed separation of umbilicus.

Chédiak-Higashi
disease

Autosomal recessive. Defect in microtubular function and lysosomal emptying of phagocytic cells. Presents with recurrent pyogenic infections by staphylococci and streptococci, partial albinism, and peripheral neuropathy.

Chronic gran-
ulomatous disease

Defect in phagocytosis of neutrophils owing to lack of NADPH oxidase activity or similar enzymes. Presents with marked susceptibility to opportunistic infections with bacteria, especially *S. aureus*, *E. coli*, and *Aspergillus*. Diagnosis confirmed with negative nitroblue tetrazolium dye reduction test.

4. Idiopathic dysfunction of:

T cells—chronic
mucocutaneous
candidiasis

T-cell dysfunction specifically against *Candida albicans*. Presents with skin and mucous membrane *Candida* infections.

B cells—selective
immunoglobulin
deficiency

Deficiency in a specific class of immunoglobulins—possibly due to a defect in isotype switching. Selective IgA deficiency is the most common selective immunoglobulin deficiency. Presents with sinus and lung infections; milk allergies and diarrhea are common.

B cells—ataxia-
telangiectasia

Defect in DNA repair enzymes with associated IgA deficiency. Presents with cerebellar problems (ataxia) and spider angiomas (telangiectasia).

Autoantibodies		Associated disorder
	Antinuclear antibodies (ANA)	SLE
	Anti-dsDNA, anti-Smith	Specific for SLE
	Antihistone	Drug-induced lupus
	Anti-IgG (rheumatoid factor)	Rheumatoid arthritis
	Antineutrophil (C-ANCA, P-ANCA)	Vasculitis
	Anticentromere	Scleroderma (CREST)
	Anti-Scl-70	Scleroderma (diffuse)
	Antimitochondrial	1° biliary cirrhosis
	Antigliadin	Celiac disease
	Anti-basement membrane	Goodpasture's syndrome
	Anti-epithelial cell	Pemphigus vulgaris
	Antimicrosomal	Hashimoto's thyroiditis
	Anti-Jo-1	Polymyositis, dermatomyositis
HLA subtypes		
B27	Psoriasis, Ankylosing spondylitis, Inflammatory bowel disease, Reiter's syndrome.	PAIR.
B8	Graves' disease, celiac sprue.	
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture's.	
DR3	Diabetes mellitus type 1.	
DR4	Rheumatoid arthritis, diabetes mellitus type 1.	
DR5	Pernicious anemia → B ₁₂ deficiency, Hashimoto's thyroiditis.	
DR7	Steroid-responsive nephrotic syndrome.	
Transplant rejection		
Hyperacute rejection	Antibody mediated due to the presence of preformed antidonor antibodies in the transplant recipient. Occurs within minutes after transplantation.	
Acute rejection	Cell mediated due to cytotoxic T lymphocytes reacting against foreign MHCs. Occurs weeks after transplantation. Reversible with immunosuppressants such as cyclosporin and OKT3.	
Chronic rejection	Antibody-mediated vascular damage (fibrinoid necrosis); occurs months to years after transplantation. Irreversible.	
Graft-versus-host disease	Grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with "foreign" proteins, resulting in severe organ dysfunction. Major symptoms include a maculopapular rash, jaundice, hepatosplenomegaly, and diarrhea.	

This image shows a full page of blank, lined paper. It features approximately 28 horizontal blue or grey lines spaced evenly apart, typical of notebook paper. The lines extend across the entire width of the page, leaving small margins at the top and bottom. There are no vertical lines, text, or other markings on the page.

HIGH-YIELD PRINCIPLES IN

Pharmacology

“Take me, I am the drug; take me, I am hallucinogenic.”

—Salvador Dali

“I was under medication when I made the decision not to burn the tapes.”

—Richard Nixon

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

- ▶ High-Yield Clinical Vignettes
- ▶ Pharmacodynamics
- ▶ Autonomic Drugs
- ▶ Toxicities and Side Effects
- ▶ Miscellaneous

PHARMACOLOGY—HIGH-YIELD CLINICAL VIGNETTES

- | | | |
|--|---|--|
| ■ 28-year-old chemist presents with MPTP exposure. | What neurotransmitter is depleted? | Dopamine. |
| ■ Woman taking tetracycline exhibits photosensitivity. | What are the clinical manifestations? | Rash on sun-exposed regions of the body. |
| ■ African-American man who goes to Africa develops a hemolytic anemia after taking malarial prophylaxis. | What is the enzyme deficiency? | Glucose-6-phosphate dehydrogenase. |
| ■ Farmer presents with dyspnea, salivation, miosis, diarrhea, cramping, and blurry vision. | What caused this, and what is the mechanism of action? | Insecticide poisoning; inhibition of acetylcholinesterase. |
| ■ 27-year-old female with a history of psychiatric illness now has urinary retention due to a neuroleptic. | What do you treat it with? | Bethanechol. |
| ■ Patient with recent kidney transplant is on cyclosporine for immunosuppression. Requires antifungal agent for candidiasis. | What antifungal drug would result in cyclosporine toxicity? | Ketoconazole. |
| ■ Patient is on carbamazepine. | What routine workup should always be done? | LFTs. |
| ■ 23-year-old female who is on rifampin for TB prophylaxis and on birth control (estrogen) gets pregnant. | Why? | Rifampin augments estrogen metabolism in the liver, rendering it less effective. |

Pharmacokinetics

Volume of distribution (V_d)	Relates the amount of drug in the body to the plasma concentration. V_d of plasma protein-bound drugs can be altered by liver and kidney disease.
	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$
Clearance (CL)	Relates the rate of elimination to the plasma concentration.
	$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}}$
Half-life ($t_{1/2}$)	The time required to change the amount of drug in the body by $\frac{1}{2}$ during elimination (or during a constant infusion). A drug infused at a constant rate reaches about 94% of steady state after $4 t_{1/2}$.

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

# of half-lives	1	2	3	3.3
Concentration	50%	75%	87.5%	90%

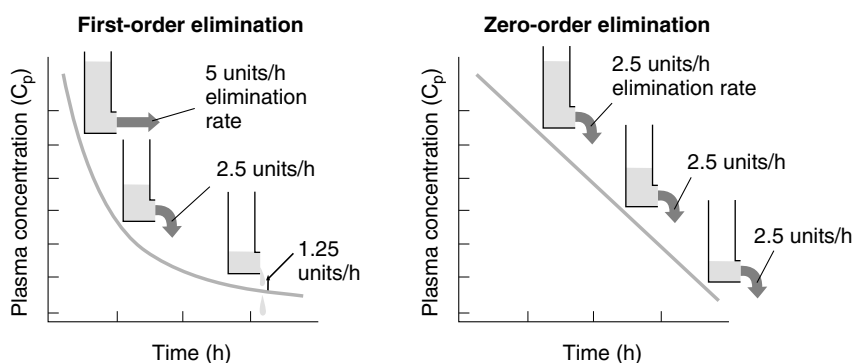
Dosage calculations

Loading dose = $C_p \times V_d / F$.
 Maintenance dose = $C_p \times CL / F$
 where C_p = target plasma concentration
 and F = bioavailability.

In patients with impaired renal or hepatic function, the loading dose remains unchanged, although the maintenance dose is ↓.

Elimination of drugs

Zero-order elimination	Rate of elimination is constant regardless of C (i.e., constant amount of drug eliminated per unit time). C_p ↓ linearly with time. Examples of drugs—ethanol, phenytoin, and aspirin (at high or toxic concentrations).
First-order elimination	Rate of elimination is proportional to the drug concentration (i.e., constant fraction of drug eliminated per unit time). C_p ↓ exponentially with time.



In drugs with first-order kinetics (see left panel above), rate of elimination is proportional to plasma concentration (C_p); in the case of zero-order elimination (right panel), the rate is constant and independent of concentration.

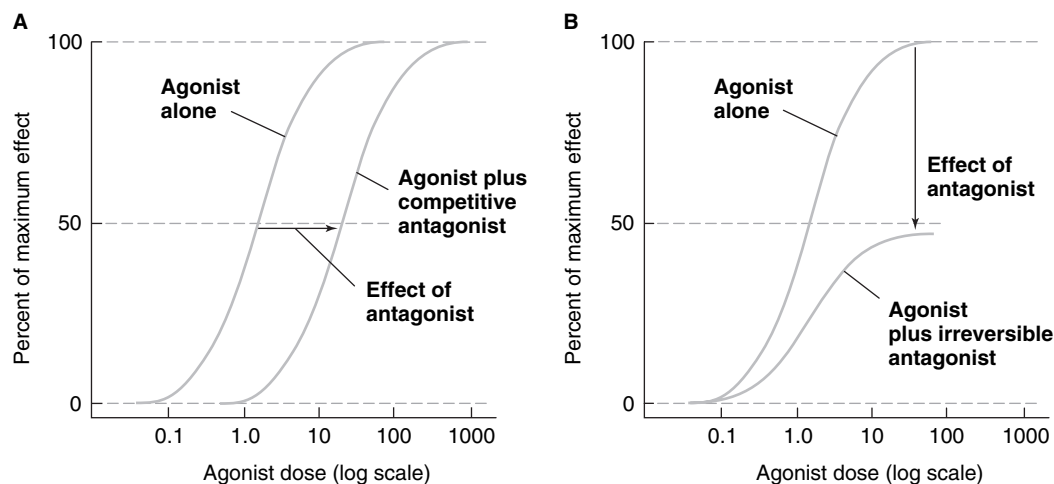
(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:5.)

► PHARMACOLOGY—PHARMACODYNAMICS (*continued*)**Phase I vs. phase II metabolism**

Phase I (reduction, oxidation, hydrolysis) yields slightly polar, water-soluble metabolites (often still active).

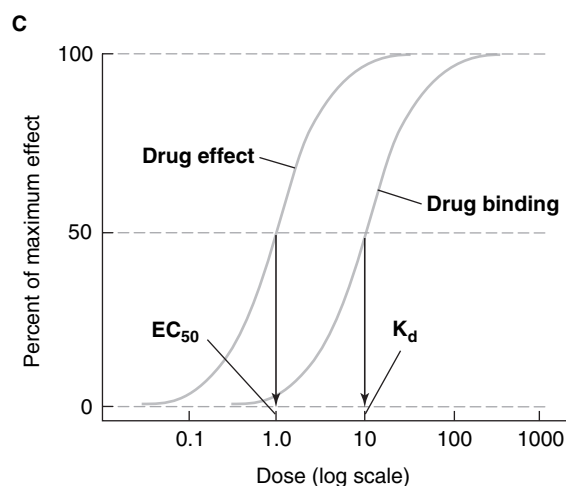
Phase II (acetylation, glucuronidation, sulfation) yields very polar, inactive metabolites (renally excreted).

Phase I—cytochrome P-450.
Phase II—conjugation.
Geriatric patients lose phase I first.

Pharmacodynamics

(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:13–14.)

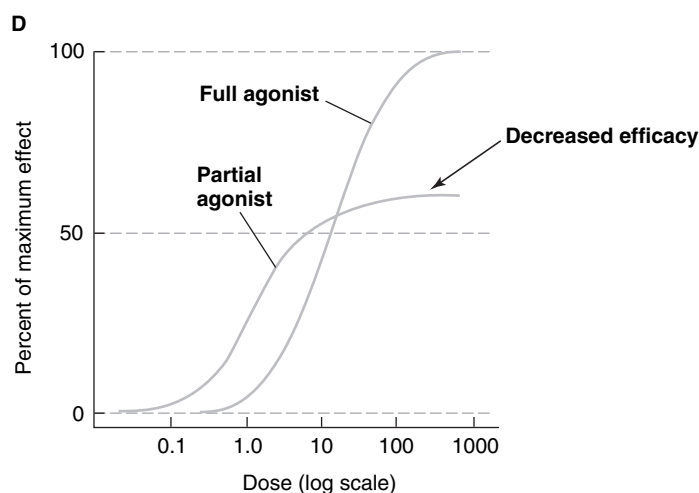
Shown above are agonist dose-response curves in the presence of competitive and irreversible antagonists. Note the use of a logarithmic scale for drug concentration. **A.** A competitive antagonist has an effect illustrated by the shift of the agonist curve to the right. **B.** A noncompetitive antagonist shifts the agonist curve downward.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:13.)

- C. In a system with spare receptors, the EC_{50} is lower than the K_d , indicating that to achieve 50% of maximum effect, < 50% of the receptors must be activated. EC_{50} : dose causing 50% of maximal effect. K_d : concentration of drug required to bind 50% of receptor sites.

Pharmacodynamics (continued)



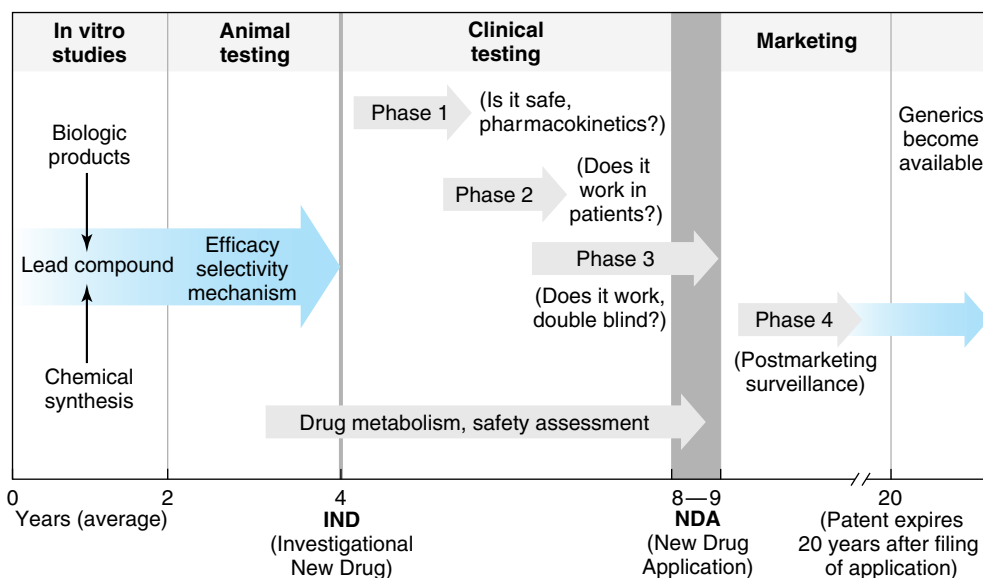
(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:13.)

- D. Comparison of dose-response curves for a full agonist and a partial agonist. The partial agonist acts on the same receptor system as the full agonist but cannot produce an equivalently large effect (it has lower maximal efficacy) no matter how much the dose is increased. A partial agonist may be more potent (as in the figure), less potent, or equally potent; potency is an independent factor.

Therapeutic index

$$\frac{TD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

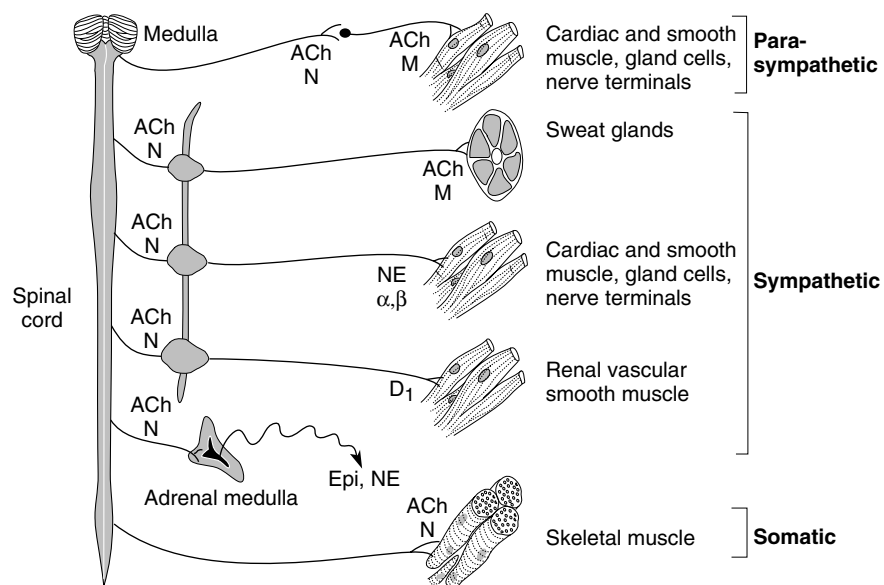
Drug development



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:365.)

► PHARMACOLOGY—AUTONOMIC DRUGS

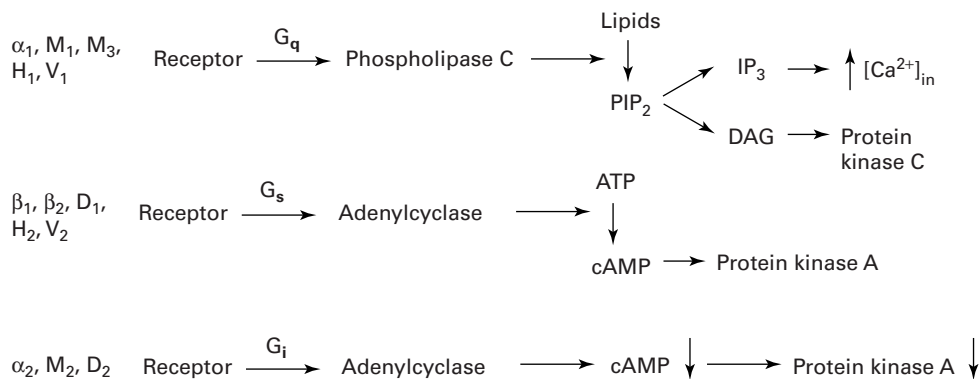
Central and peripheral nervous system



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:74.)

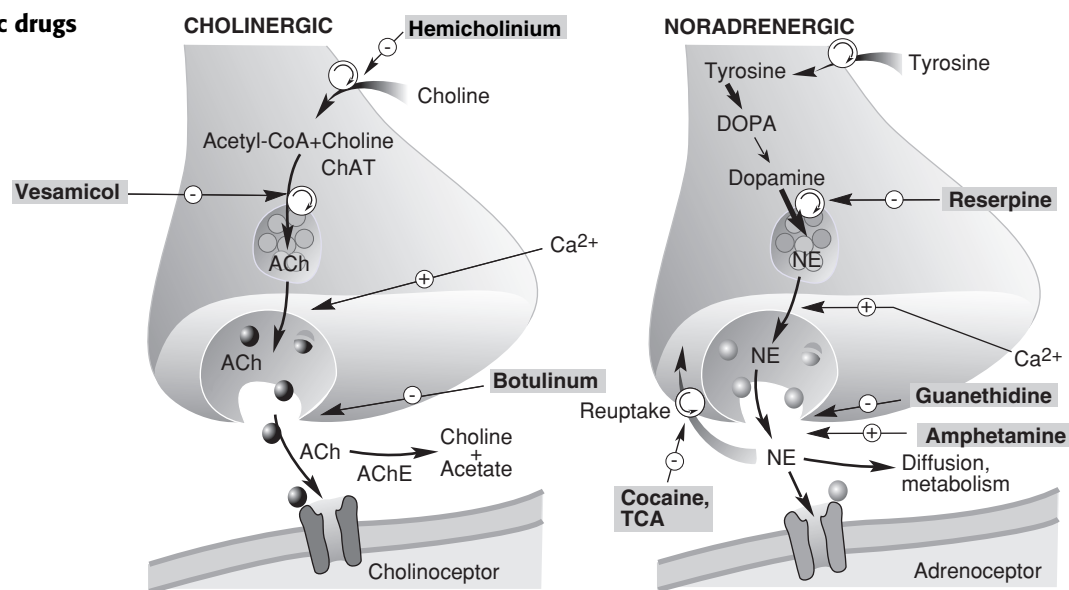
G-protein-linked 2nd messengers

Receptor	G-protein class	Major functions
α_1	q	\uparrow vascular smooth muscle contraction
α_2	i	\downarrow sympathetic outflow, \downarrow insulin release
β_1	s	\uparrow heart rate, \uparrow contractility, \uparrow renin release, \uparrow lipolysis, \uparrow aqueous humor formation
β_2	s	Vasodilation, bronchodilation, \uparrow glucagon release
M_1	q	CNS
M_2	i	\downarrow heart rate
M_3	q	\uparrow exocrine gland secretions
D_1	s	Relaxes renal vascular smooth muscle
D_2	i	Modulates transmitter release, especially in brain
H_1	q	\uparrow nasal and bronchial mucus production, contraction of bronchioles, pruritus, and pain
H_2	s	\uparrow gastric acid secretion
V_1	q	\uparrow vascular smooth muscle contraction
V_2	s	\uparrow H_2O permeability and reabsorption in the collecting tubules of the kidney



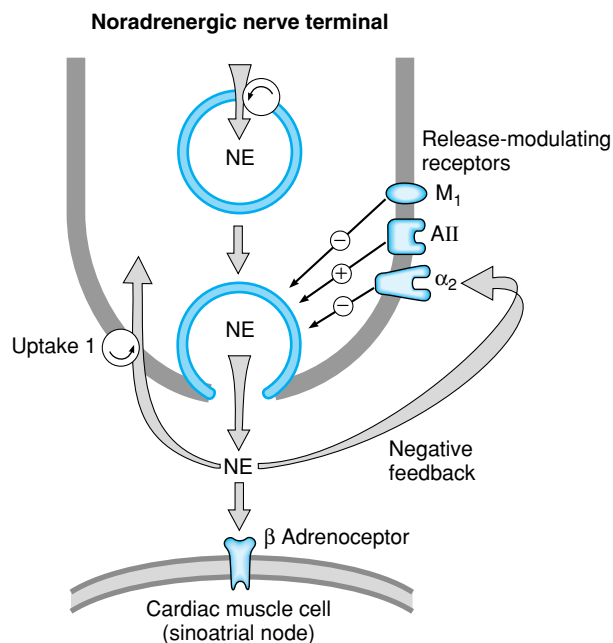
► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)

Autonomic drugs



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:42.)

Circles with rotating arrows represent transporters; ChAT, choline acetyltransferase; ACh, acetylcholine; AChE, acetylcholinesterase; NE, norepinephrine.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:42.)

Release of NE from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α₂ autoreceptors, and by ACh, angiotensin II, and other substances.

Cholinomimetics

Drug	Clinical applications	Action
Direct agonists		
Bethanechol	Postoperative and neurogenic ileus and urinary retention	Activates Bowel and Bladder smooth muscle; resistant to AChE
Carbachol, pilocarpine	Glaucoma	Activates ciliary muscle of eye (open angle), pupillary sphincter (narrow angle); resistant to AChE
Indirect agonists (anticholinesterases)		
Neostigmine	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative)	↑ endogenous ACh
Pyridostigmine	Myasthenia gravis	↑ endogenous ACh; ↑ strength
Edrophonium	Diagnosis of myasthenia gravis (extremely short acting)	↑ endogenous ACh
Physostigmine	Glaucoma (crosses blood-brain barrier → CNS) and atropine overdose	↑ endogenous ACh
Echothiophate	Glaucoma	↑ endogenous ACh

Cholinesterase inhibitor poisoning

Symptoms include **D**iarrrhea, **U**rination, **M**iosis, **B**ronchospasm, **B**radycardia, **E**xcitation of skeletal muscle and CNS, **L**acrimation, **S**weating, and **S**alivation (also abdominal cramping).
Antidote—atropine (muscarinic antagonist) plus pralidoxime (chemical antagonist used to regenerate active cholinesterase).

DUMBBELSS.
Parathion and other organophosphates.

Cholinoreceptor blockers

Drug	Organ system	Application
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia
Benztropine	CNS	Parkinson's disease
Scopolamine	CNS	Motion sickness
Ipratropium	Respiratory	Asthma, COPD
Methscopolamine, oxybutin, glycopyrrolate	Genitourinary	Reduce urgency in mild cystitis and reduce bladder spasms

► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)**Atropine**

Muscarinic antagonist.

Organ system

Eye

↑ pupil dilation, cycloplegia.

Airway

↓ secretions.

Stomach

↓ acid secretion.

Gut

↓ motility.

Bladder

↓ urgency in cystitis.

Toxicity

↑ body temperature; rapid pulse; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation.

Can cause acute angle-closure glaucoma in elderly, urinary retention in men with prostatic hypertrophy, and hyperthermia in infants.

Blocks **SLUD**:

Salivation

Lacrimation

Urination

Defecation

Side effects:

Hot as a hare

Dry as a bone

Red as a beet

Blind as a bat

Mad as a hatter

Hexamethonium

Mechanism

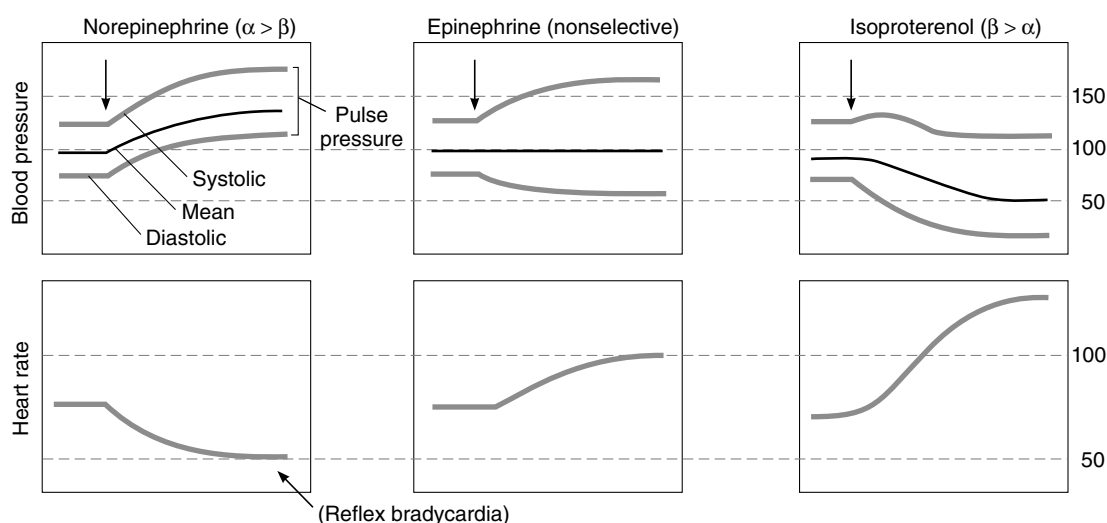
Nicotinic ACh receptor antagonist.

Clinical use

Ganglionic blocker. Used in experimental models to prevent vagal reflex responses to changes in blood pressure—e.g., prevents reflex bradycardia caused by NE.

Sympathomimetics

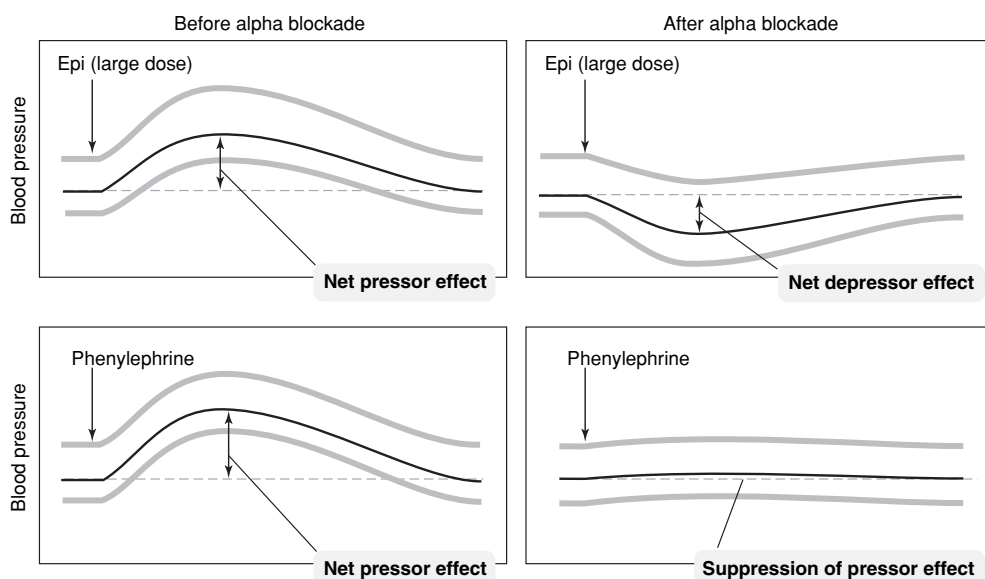
Drug	Mechanism/selectivity	Applications
Catecholamines		
Epinephrine	Direct general agonist (α_1 , α_2 , β_1 , β_2)	Anaphylaxis, glaucoma (open angle), asthma, hypotension
NE	α_1 , α_2 , β_1	Hypotension (but \downarrow renal perfusion)
Isoproterenol	$\beta_1 = \beta_2$	AV block (rare)
Dopamine	$D_1 = D_2 > \beta > \alpha$	Shock (\uparrow renal perfusion), heart failure
Dobutamine	$\beta_1 > \beta_2$	Shock, heart failure
Other		
Amphetamine	Indirect general agonist, releases stored catecholamines	Narcolepsy, obesity, attention deficit disorder
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion, urinary incontinence, hypotension
Phenylephrine	$\alpha_1 > \alpha_2$	Pupil dilator, vasoconstriction, nasal decongestion
Albuterol, terbutaline	$\beta_2 > \beta_1$	Asthma
Cocaine	Indirect general agonist, uptake inhibitor	Causes vasoconstriction and local anesthesia
Clonidine, α -methyldopa	Centrally acting α -agonist, \downarrow central adrenergic outflow	Hypertension, especially with renal disease (no \downarrow in blood flow to kidney)



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:72.)

► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*) **α -blockers**

Drugs	Application	Toxicity
Nonselective		
Phenoxybenzamine (irreversible) and phentolamine (reversible)	Pheochromocytoma	Orthostatic hypotension, reflex tachycardia
α_1 selective		
Prazosin, terazosin, doxazosin	Hypertension, urinary retention in BPH	1st-dose orthostatic hypotension, dizziness, headache
α_2 selective		
Mirtazapine	Depression	Sedation, \uparrow serum cholesterol, \uparrow appetite



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:80.)

Shown above are the effects of an α -blocker (e.g., phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net decrease (the β_2 response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a “pure” α -agonist without β action.

β-blockers	Propranolol, metoprolol, atenolol, nadolol, timolol, pindolol, esmolol, labetalol.
Application	Effect
Hypertension	\downarrow cardiac output, \downarrow renin secretion
Angina pectoris	\downarrow heart rate and contractility, resulting in \downarrow O_2 consumption
MI	β -blockers \downarrow mortality
SVT (propranolol, esmolol)	\downarrow AV conduction velocity
CHF	Slows progression of chronic failure
Glaucoma (timolol)	\downarrow secretion of aqueous humor
Toxicity	Impotence, exacerbation of asthma, cardiovascular adverse effects (bradycardia, AV block, CHF), CNS adverse effects (sedation, sleep alterations); use with caution in diabetics
Selectivity	Nonselective ($\beta_1 = \beta_2$)—propranolol, timolol, nadolol, pindolol (partial agonist), and labetalol (partial agonist) β_1 selective ($\beta_1 > \beta_2$)—Acebutolol (partial agonist), Betaxolol, Esmolol (short acting), Atenolol, Metoprolol

A BEAM of β_1 blockers.**Glaucoma drugs**

Drug	Mechanism	Side effects
α-agonists		
Epinephrine	\uparrow outflow of aqueous humor	Mydriasis, stinging; do not use in closed-angle glaucoma
Brimonidine	\downarrow aqueous humor synthesis	No pupillary or vision changes
β-blockers		
Timolol, betaxolol, carteolol	\downarrow aqueous humor secretion	No pupillary or vision changes
Diuretics		
Acetazolamide	\downarrow aqueous humor secretion due to \downarrow HCO_3^- (via inhibition of carbonic anhydrase)	No pupillary or vision changes
Cholinomimetics		
Pilocarpine, carbachol, physostigmine, echothiophate	\uparrow outflow of aqueous humor; contract ciliary muscle and open trabecular meshwork	Miosis, cyclospasm
Prostaglandin		
Latanoprost ($PGF_{2\alpha}$)	\uparrow outflow of aqueous humor	Darkens color of iris (browning)

► PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

Specific antidotes	Toxin	Antidote/treatment
	1. Acetaminophen	1. N-acetylcysteine
	2. Salicylates	2. Alkalinize urine, dialysis
	3. Anticholinesterases, organophosphates	3. Atropine, pralidoxime
	4. Antimuscarinic, anticholinergic agents	4. Physostigmine salicylate
	5. β -blockers	5. Glucagon
	6. Digitalis	6. Stop dig, normalize K^+ , lidocaine, anti-dig Fab fragments, Mg^{2+}
	7. Iron	7. Deferoxamine
	8. Lead	8. CaEDTA, dimercaprol, succimer, penicillamine
	9. Arsenic, mercury, gold	9. Dimercaprol (BAL), succimer
	10. Copper, arsenic, gold	10. Penicillamine
	11. Cyanide	11. Nitrite, hydroxocobalamin, thiosulfate
	12. Methemoglobin	12. Methylene blue
	13. Carbon monoxide	13. 100% O_2 , hyperbaric O_2
	14. Methanol, ethylene glycol (antifreeze)	14. Ethanol, dialysis, fomepizole
	15. Opioids	15. Naloxone/naltrexone
	16. Benzodiazepines	16. Flumazenil
	17. TCAs	17. $NaHCO_3$ (nonspecific)
	18. Heparin	18. Protamine
	19. Warfarin	19. Vitamin K, fresh frozen plasma
	20. tPA, streptokinase	20. Aminocaproic acid
Lead poisoning	Lead Lines on gingivae and on epiphyses of long bones on x-ray. Encephalopathy and Erythrocyte basophilic stippling. Abdominal colic and sideroblastic Anemia. Drops—wrist and foot drop. Dimercaprol and EDTA 1st line of treatment. Succimer for kids.	LEAD. High risk in houses with chipped paint. It “sucks” to be a kid who eats lead.
Urine pH and drug elimination	Weak acids (phenobarbital, methotrexate, aspirin) alkalinize urine with bicarbonate to \uparrow clearance. Weak bases (amphetamines) acidify urine to \uparrow clearance (give NH_4Cl).	

Drug reactions

Drug reaction by system	Causal agent
Cardiovascular	
Atropine-like side effects	Tricyclics
Cardiac toxicity	Doxorubicin (Adriamycin), daunorubicin
Coronary vasospasm	Cocaine
Cutaneous flushing	Niacin, Ca ²⁺ channel blockers, adenosine, vancomycin
Torsades de pointes	Class III (sotalol), class IA (quinidine) antiarrhythmics, cisapride
Hematologic	
Agranulocytosis	Clozapine, carbamazepine, colchicine
Aplastic anemia	Chloramphenicol, benzene, NSAIDs
Gray baby syndrome	Chloramphenicol
Hemolysis in G6PD-deficient patients	Sulfonamides, isoniazid (INH), aspirin, ibuprofen, primaquine, nitrofurantoin
Thrombotic complications	OCPs (e.g., estrogens and progestins)
Respiratory	
Cough	ACE inhibitors (losartan—no cough)
Pulmonary fibrosis	Bleomycin, amiodarone, busulfan
GI	
Acute cholestatic hepatitis	Macrolides
Focal to massive hepatic necrosis	Halothane, valproic acid, acetaminophen, <i>Amanita phalloides</i>
Hepatitis	INH
Pseudomembranous colitis	Clindamycin, ampicillin
Reproductive/endocrine	
Adrenocortical insufficiency	Glucocorticoid withdrawal (HPA suppression)
Gynecomastia	Spironolactone, Digitalis, Cimetidine, chronic Alcohol use, estrogens, Ketoconazole (Some Drugs Create Awesome Knockers)
Hot flashes	Tamoxifen
Musculoskeletal/connective tissue	
Gingival hyperplasia	Phenytoin
Osteoporosis	Corticosteroids, heparin
Photosensitivity	Sulfonamides, Amiodarone, Tetracycline (SAT for a photo)
SLE-like syndrome	Hydralazine, INH, Procainamide, Phenytoin (it's not HIPP to have lupus)
Tendonitis, tendon rupture, and cartilage damage (kids)	Fluoroquinolones
Renal	
Fanconi's syndrome	Expired tetracycline
Interstitial nephritis	Methicillin
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide

► PHARMACOLOGY–TOXICITIES AND SIDE EFFECTS (*continued*)**Drug reactions (*continued*)****Neurologic**

Cinchonism	Quinidine, quinine
Diabetes insipidus	Lithium, demeclocycline
Seizures	Bupropion, imipenem/cilastatin
Tardive dyskinesia	Antipsychotics

Multiorgan

Disulfiram-like reaction	Metronidazole, certain cephalosporins, procarbazine, sulfonyleureas
Nephrotoxicity/neurotoxicity	Polymyxins
Nephrotoxicity/ototoxicity	Aminoglycosides, loop diuretics, cisplatin

P-450 interactions**Inducers**

Quinidine
Barbiturates
Phenytoin
Rifampin
Griseofulvin
Carbamazepine

Inhibitors

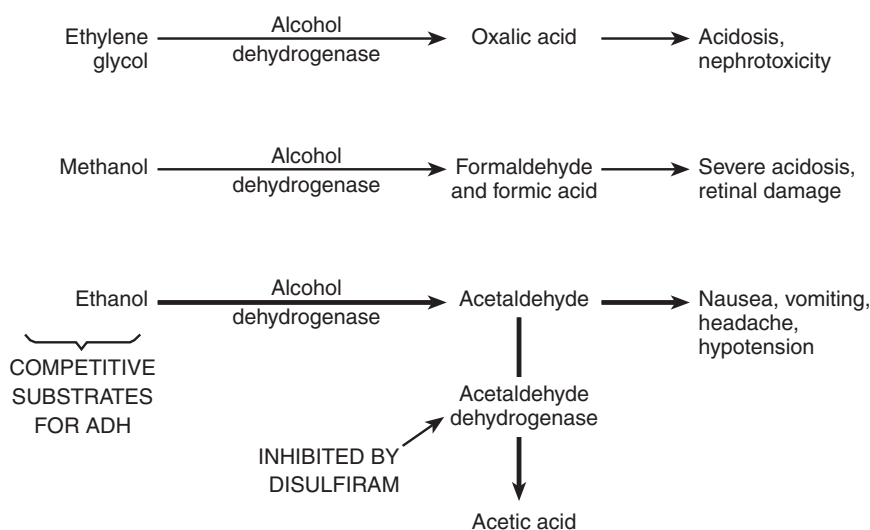
Isoniazid
Sulfonamides
Cimetidine
Ketoconazole
Erythromycin
Grapefruit juice
St. John's wort

Inducers:

Queen Barb takes Phen-phen
and Refuses Greasy Carbs.

Inhibitors:

Inhibitors Stop Cyber-Kids
from Eating GrapefruitS.

Alcohol toxicity

Herbal agents

Agent	Clinical uses	Toxicities
Echinacea	Common cold	GI distress, dizziness, and headache
Ephedra	As for ephedrine	CNS and cardiovascular stimulation; arrhythmias, stroke, and seizures at high doses
Feverfew	Migraine	GI distress, mouth ulcers, antiplatelet actions
Ginkgo	Intermittent claudication	GI distress, anxiety, insomnia, headache, antiplatelet actions
Kava	Chronic anxiety	GI distress, sedation, ataxia, hepatotoxicity, phototoxicity, dermatotoxicity
Milk thistle	Viral hepatitis	Loose stools
Saw palmetto	Benign prostatic hyperplasia	GI distress, ↓ libido, hypertension
St. John's wort	Mild to moderate depression	GI distress and phototoxicity; serotonin syndrome with SSRIs; inhibits P-450 system
Dehydroepiandrosterone	Symptomatic improvement in females with SLE or AIDS	Androgenization (premenopausal women), estrogenic effects (postmenopausal), feminization (young men)
Melatonin	Jet lag, insomnia	Sedation, suppresses midcycle LH, hypoprolactinemia

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003.)

Drug name

Ending	Category	Example
-afil	Erectile dysfunction	Sildenafil
-ane	Inhalational general anesthetic	Halothane
-azepam	Benzodiazepine	Diazepam
-azine	Phenothiazine (neuroleptic, antiemetic)	Chlorpromazine
-azole	Antifungal	Ketoconazole
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-cillin	Penicillin	Methicillin
-cycline	Antibiotic, protein synthesis inhibitor	Tetracycline
-ipramine	TCA	Imipramine
-navir	Protease inhibitor	Saquinavir
-olol	β-antagonist	Propranolol
-operidol	Butyrophenone (neuroleptic)	Haloperidol
-oxin	Cardiac glycoside (inotropic agent)	Digoxin
-phylline	Methylxanthine	Theophylline
-pril	ACE inhibitor	Captopril
-terol	β ₂ agonist	Albuterol
-tidine	H ₂ antagonist	Cimetidine
-triptyline	TCA	Amitriptyline
-tropin	Pituitary hormone	Somatotropin
-zosin	α ₁ antagonist	Prazosin

NOTES

SECTION III

High-Yield Organ Systems

- ▶ Approaching the Organ Systems
- ▶ Cardiovascular
- ▶ Endocrine
- ▶ Gastrointestinal
- ▶ Hematology and Oncology
- ▶ Musculoskeletal and Connective Tissue
- ▶ Neurology and Psychiatry
- ▶ Renal
- ▶ Reproductive
- ▶ Respiratory

In this section, we have divided the High-Yield Facts into the major **Organ Systems**. Within each Organ System are several subsections, including **Anatomy**, **Physiology**, **Pathology**, and **Pharmacology**. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a “vertical” framework for learning. Below is some general advice for studying the organ systems by these subsections.

Anatomy

Several topics fall under this heading, including embryology, gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy related to specific diseases (e.g., Pancoast’s tumor, Horner’s syndrome), traumatic injuries (e.g., fractures, sensory and motor nerve deficits), procedures (e.g., lumbar puncture), and common surgeries (e.g., cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (e.g., sagittal brain MRI; axial CT of midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy) also has good yield. Use this as an opportunity to learn associated neuropathology and neurophysiology. Basic embryology (especially congenital malformations) is worth reviewing as well.

Physiology

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (e.g., Fick equation, clearance equations). You are seldom asked to perform complex calculations. Hormones are the focus of many questions. Learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is now clinically relevant and involves understanding physiologic changes associated with pathologic processes (e.g., changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (e.g., heart, lungs, kidneys, GI tract) and endocrine glands.

Pathology

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material. Review the basic principles and hallmark characteristics of the key diseases. Given the increasingly clinical orientation of Step 1, it is no longer enough to know only the “trigger word” associations of certain diseases (e.g., café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of the major diseases having a high prevalence in the United States (e.g., alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

Pharmacology

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

Cardiovascular

“As for me, except for an occasional heart attack, I feel as young as I ever did.”

—Robert Benchley

“Hearts will never be practical until they are made unbreakable.”

—*The Wizard of Oz*

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

■ Pregnant woman in 3rd trimester has normal blood pressure when standing and sitting. When supine, blood pressure drops to 90/50.	What is the diagnosis?	Compression of the IVC.
■ 35-year-old man has high blood pressure in his arms and low pressure in his legs.	What is the diagnosis?	Coarctation of the aorta.
■ 5-year-old boy presents with systolic murmur and wide, fixed split S2.	What is the diagnosis?	ASD.
■ During a game, a young football player collapses and dies immediately.	What is the most likely type of cardiac disease?	Hypertrophic cardiomyopathy.
■ Patient has a stroke after incurring multiple long bone fractures in trauma stemming from a motor vehicle accident.	What caused the infarct?	Fat emboli.
■ Elderly woman presents with a headache and jaw pain. Labs show elevated ESR.	What is the diagnosis?	Temporal arteritis.
■ 80-year-old man presents with a systolic crescendo-decrescendo murmur.	What is the most likely cause?	Aortic stenosis.
■ Man starts a medication for hyperlipidemia. He then develops a rash, pruritus, and GI upset.	What drug was it?	Niacin.
■ Patient develops a cough and must discontinue captopril.	What is a good replacement drug, and why doesn't it have the same side effects?	Losartan, an angiotensin II receptor antagonist, does not ↑ bradykinin as captopril does.

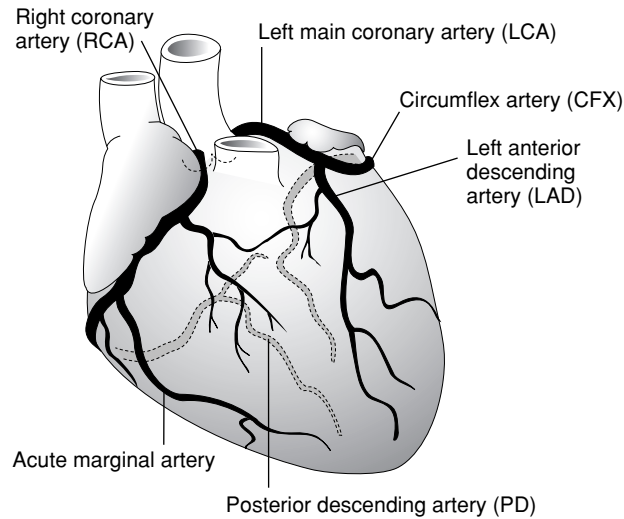
Carotid sheath

3 structures inside:

1. Internal jugular Vein (lateral)
2. Common carotid Artery (medial)
3. Vagus Nerve (posterior)

VAN.

Coronary artery anatomy



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 19th ed. Stamford, CT: Appleton & Lange, 1999:592.)

In the majority of cases, the SA and AV nodes are supplied by the RCA. 80% of the time, the RCA supplies the inferior portion of the left ventricle via the PD artery (= right dominant).

Coronary artery occlusion occurs most commonly in the LAD, which supplies the anterior interventricular septum.

Coronary arteries fill during diastole.

The most posterior part of the heart is the left atrium; enlargement can cause dysphagia.

Cardiac output (CO)

Cardiac output (CO) = (stroke volume) × (heart rate).
Fick principle:

$$CO = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$$

$$\text{Mean arterial pressure} = \left(\frac{\text{cardiac output}}{\text{output}} \right) \times \left(\frac{\text{total peripheral resistance}}{\text{resistance}} \right)$$

MAP = $\frac{1}{3}$ systolic + $\frac{2}{3}$ diastolic.

Pulse pressure = systolic – diastolic.

Pulse pressure \approx stroke volume.

$$SV = \frac{CO}{HR} = EDV - ESV$$

During exercise, CO \uparrow initially as a result of an \uparrow in SV. After prolonged exercise, CO \uparrow as a result of an \uparrow in HR.

If HR is too high, diastolic filling is incomplete and CO \downarrow (e.g., ventricular tachycardia).

Cardiac output variables

Stroke Volume affected by Contractility, Afterload, and Preload. \uparrow SV when \uparrow preload, \downarrow afterload, or \uparrow contractility.

Contractility (and SV) \uparrow with:

1. Catecholamines (\uparrow activity of Ca^{2+} pump in sarcoplasmic reticulum)
2. \uparrow intracellular calcium
3. \downarrow extracellular sodium
4. Digitalis (\uparrow intracellular Na^+ , resulting in \uparrow Ca^{2+})

Contractility (and SV) \downarrow with:

1. β_1 blockade
2. Heart failure
3. Acidosis
4. Hypoxia/hypercapnea
5. Ca^{2+} channel blockers

SV CAP.

SV \uparrow in anxiety, exercise, and pregnancy.

A failing heart has \downarrow SV.

Myocardial O_2 demand is \uparrow by:

1. \uparrow afterload (\propto diastolic BP)
2. \uparrow contractility
3. \uparrow heart rate
4. \uparrow heart size (\uparrow wall tension)

Preload and afterload

Preload = ventricular EDV.

Afterload = systolic arterial pressure (proportional to peripheral resistance).

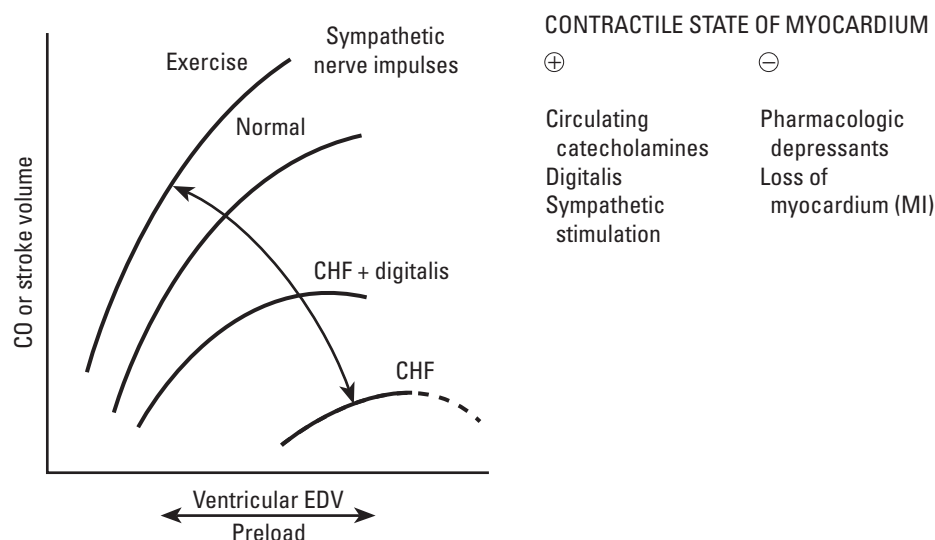
Venous dilators (e.g., nitroglycerin) \downarrow preload.

Vasodilators (e.g., hydralazine) \downarrow afterload.

Preload \uparrow with exercise (slightly), \uparrow blood volume (overtransfusion), and excitement (sympathetics).
Preload pumps up the heart.

Starling curve

Force of contraction is proportional to initial length of cardiac muscle fiber (preload).

**Ejection fraction**

$$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

EF is an index of ventricular contractility.

EF is normally $\geq 55\%$.

Resistance, pressure, flow

$$\Delta P = Q \times R$$

Similar to Ohm's law: $V = IR$.

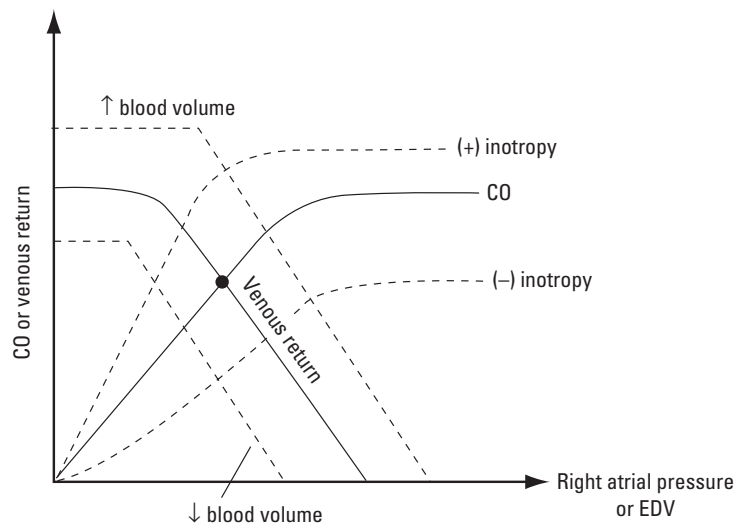
$$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

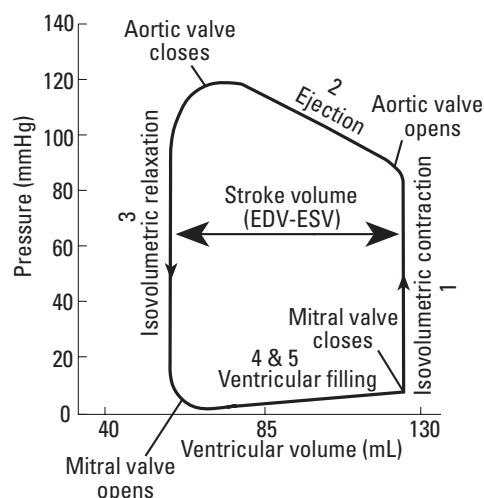
Viscosity depends mostly on hematocrit.

Viscosity \uparrow in:

1. Polycythemia
2. Hyperproteinemic states (e.g., multiple myeloma)
3. Hereditary spherocytosis

Resistance is directly proportional to viscosity and inversely proportional to the radius to the 4th power.

Cardiac and vascular function curves

► CARDIOVASCULAR—PHYSIOLOGY (*continued*)**Cardiac cycle****Phases:**

1. Isovolumetric contraction—period between mitral valve closure and aortic valve opening; period of highest O_2 consumption
2. Systolic ejection—period between aortic valve opening and closing
3. Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
4. Rapid filling—period just after mitral valve opening
5. Slow filling—period just before mitral valve closure

Sounds:

- S1—mitral and tricuspid valve closure.
 S2—aortic and pulmonary valve closure.
 S3—at end of rapid ventricular filling.
 S4—high atrial pressure/stiff ventricle.

S3 is associated with dilated CHF.

S4 (“atrial kick”) is associated with a hypertrophic ventricle.

a wave—atrial contraction.

c wave—RV contraction (tricuspid valve bulging into atrium).

v wave—↑ atrial pressure due to filling against closed tricuspid valve.

Jugular venous distention is seen in right heart failure.

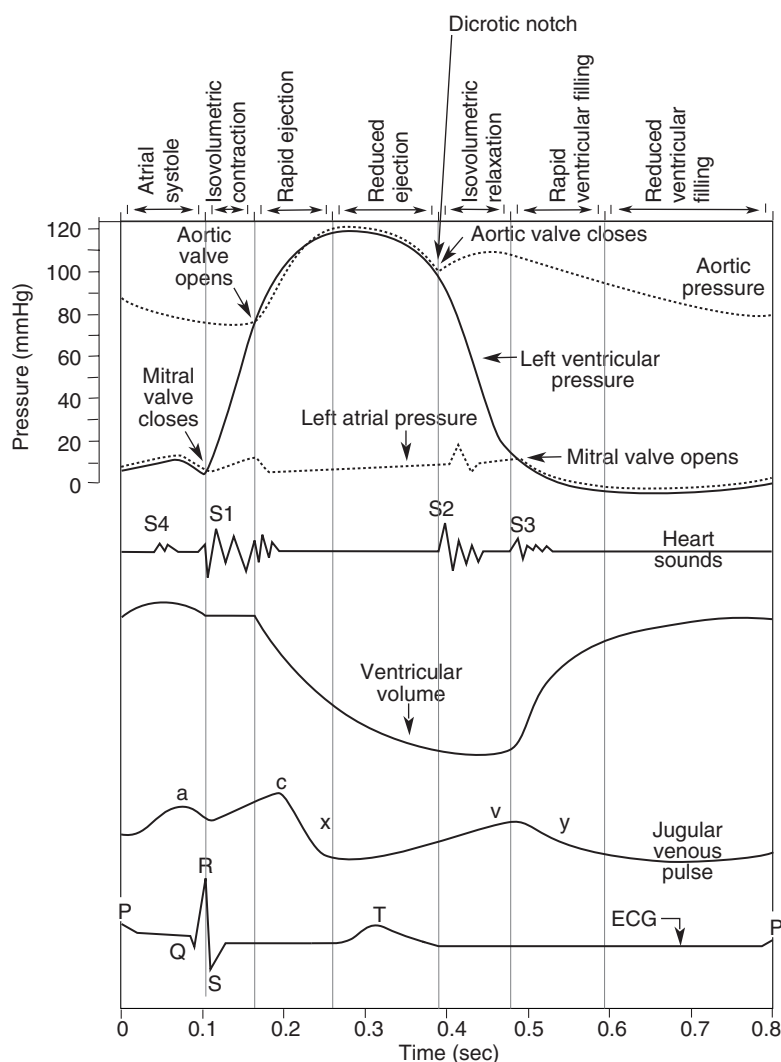
S2 splitting: aortic valve closes before pulmonic; inspiration ↑ this difference.

Normal splitting:

		A_2	P_2
		└──┘	
S1		S2	

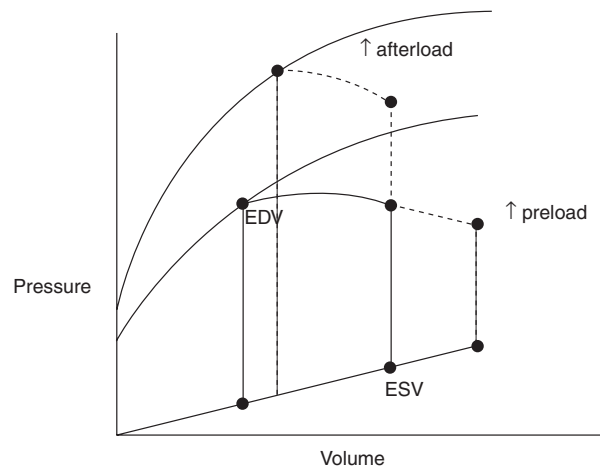
Paradoxical splitting (associated with aortic stenosis):

		P_2	A_2
Expiration			
		└──┘	
		P_2	A_2
Inspiration			
		└──┘	
S1		S2	



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. McGraw-Hill, 2005.)

Pressure-volume relationship



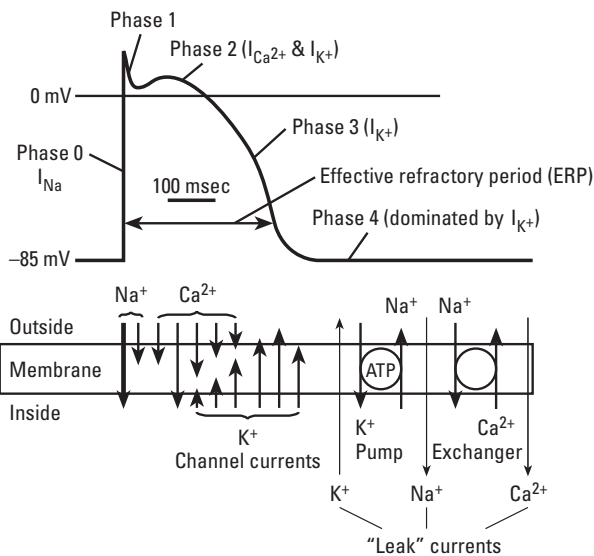
Cardiac myocyte physiology

Cardiac muscle contraction is dependent on extracellular calcium, which enters the cells during plateau of action potential and stimulates calcium release from the cardiac muscle sarcoplasmic reticulum (calcium-induced calcium release).

In contrast to skeletal muscle:

1. Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx
2. Cardiac nodal cells spontaneously depolarize, resulting in automaticity
3. Cardiac myocytes are electrically coupled to each other by gap junctions

Myocardial action potential



Occurs in atrial and ventricular myocytes and Purkinje fibers.

Phase 0 = rapid upstroke—voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.

Phase 2 = plateau— Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers another Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction.

Phase 3 = rapid repolarization—massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

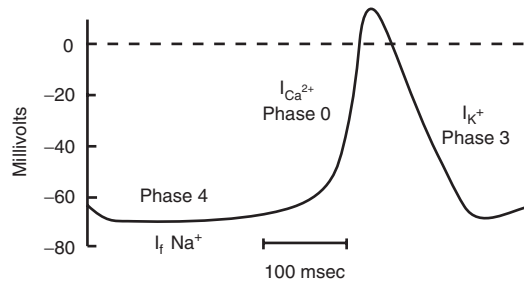
Pacemaker action potential

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

Phase 0 = upstroke—opening of voltage-gated Ca^{2+} channels. These cells lack fast voltage-gated Na^{+} channels. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

Phase 2 = plateau is absent.

Phase 4 = slow diastolic depolarization—membrane potential spontaneously depolarizes as Na^{+} conductance \uparrow (I_f different from I_{Na} above). Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines heart rate. ACh \downarrow and catecholamines \uparrow the rate of diastolic depolarization, decreasing or increasing heart rate, respectively.



(Adapted, with permission, from Ganong WF et al. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

Electrocardiogram

P wave—atrial depolarization.

PR segment—conduction delay through AV node (normally < 200 msec).

QRS complex—ventricular depolarization (normally < 120 msec).

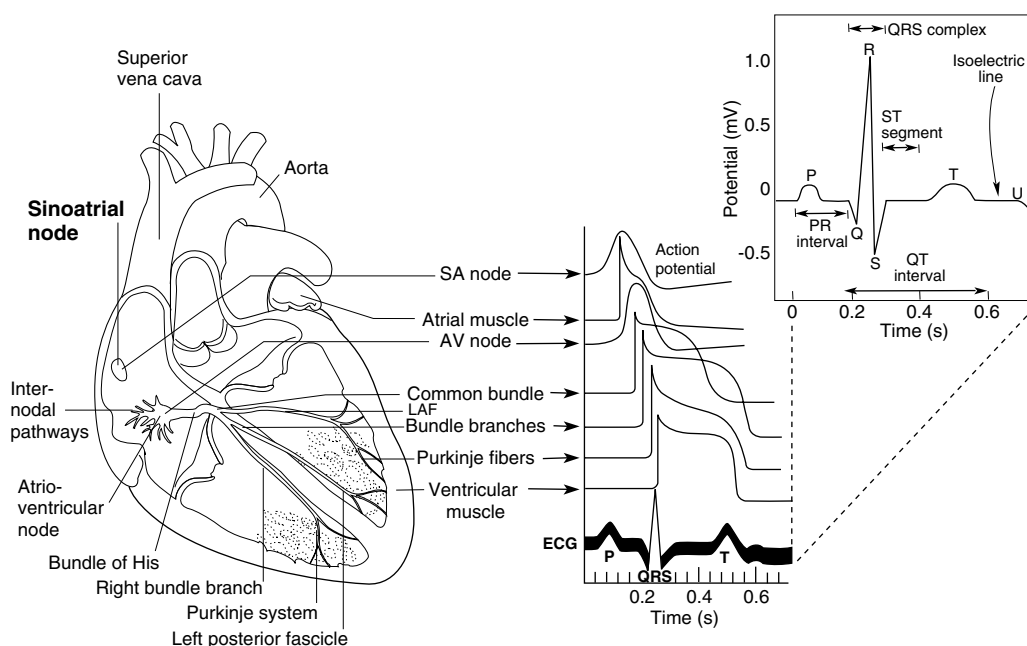
QT interval—mechanical contraction of the ventricles.

T wave—ventricular repolarization.

Atrial repolarization is masked by QRS complex.

ST segment—isolectric, ventricles depolarized.

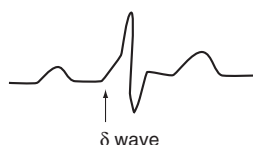
U wave—caused by hypokalemia.



SA node "pacemaker" inherent dominance with slow phase of upstroke

AV node - 100-msec delay - atrioventricular delay

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

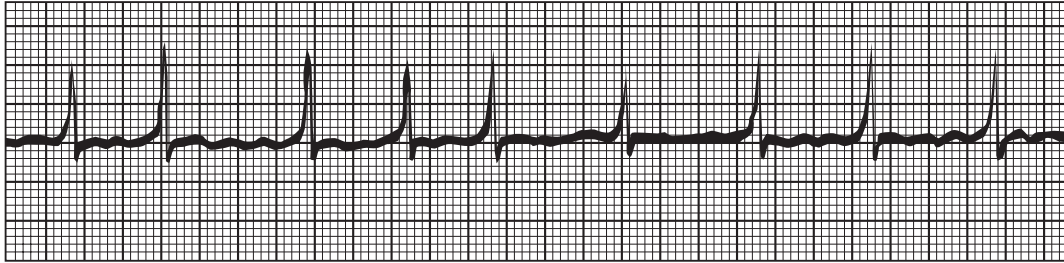
Wolff-Parkinson-White syndrome

Accessory conduction pathway from atria to ventricle (bundle of Kent), bypassing AV node. As a result, ventricles begin to partially depolarize earlier, giving rise to characteristic delta wave on ECG. May result in reentry current leading to supraventricular tachycardia.

ECG tracings

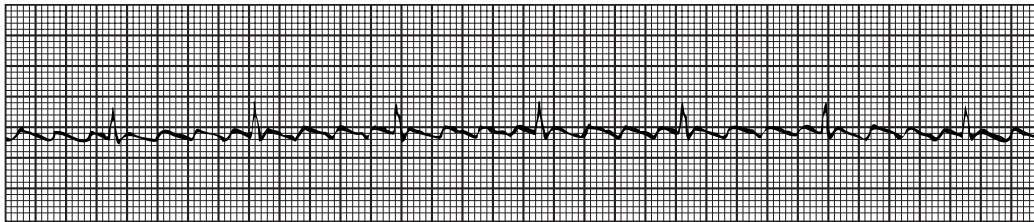
Atrial fibrillation

Chaotic and erratic baseline (irregularly irregular) with no discrete P waves in between irregularly spaced QRS complexes.



Atrial flutter

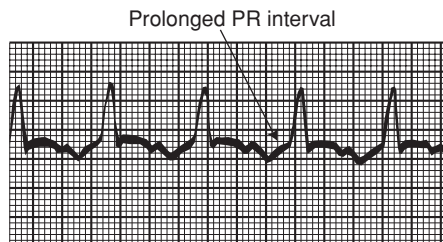
A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the “sawtooth” appearance of the flutter waves.



AV block

1st degree

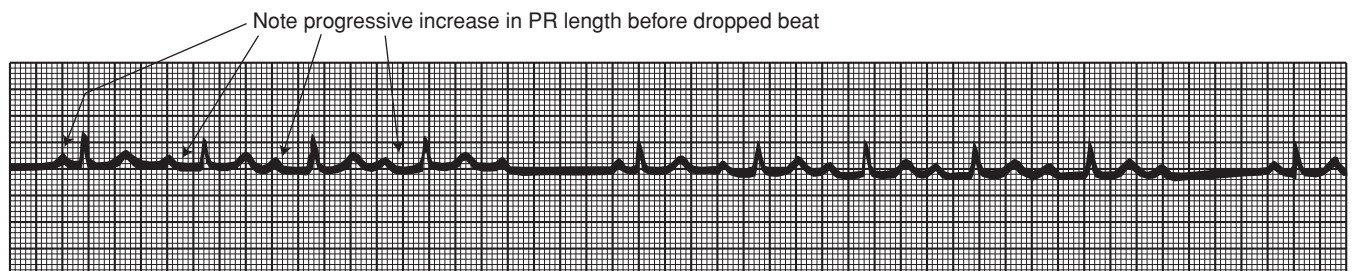
The PR interval is prolonged (> 200 msec). Asymptomatic.



2nd degree

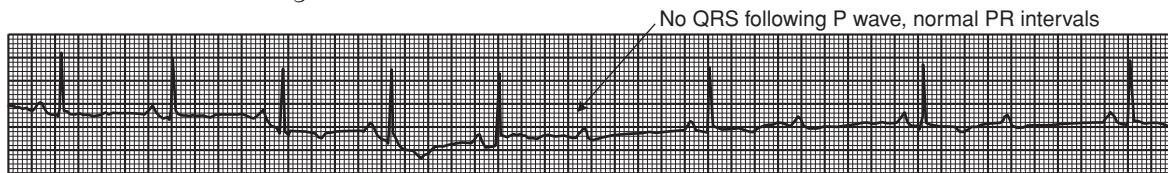
Mobitz type I (Wenckebach)

Progressive lengthening of the PR interval until a beat is “dropped” (a P wave not followed by a QRS complex). Usually asymptomatic.

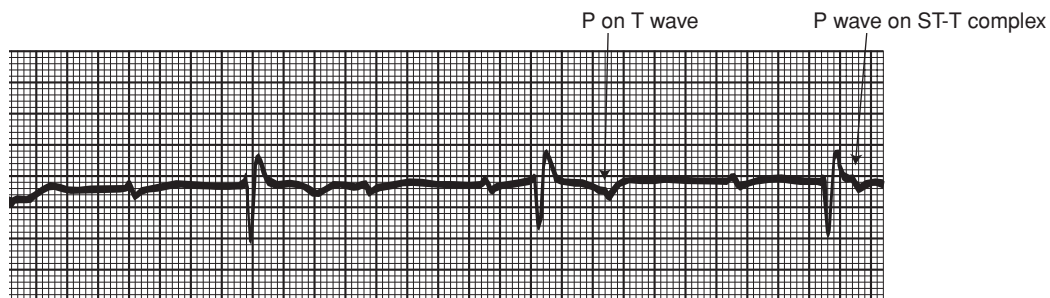


ECG tracings (continued)

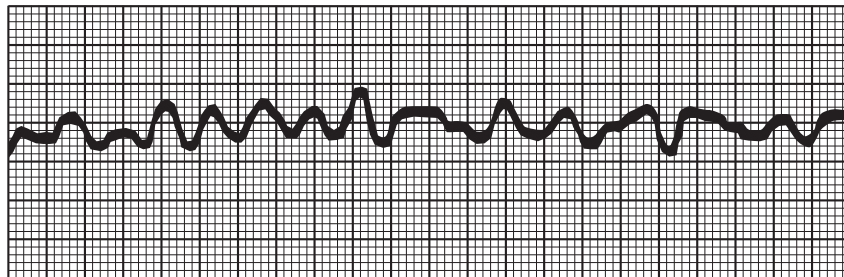
Mobitz type II Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). These abrupt, nonconducted P waves result in a pathologic condition. It is often found as 2:1 block, where there are 2 P waves to 1 QRS response. May progress to 3rd-degree block.



3rd degree (complete) The atria and ventricles beat independently of each other. Both P waves and QRS complexes are present, although the P waves bear no relation to the QRS complexes. The atrial rate is faster than the ventricular rate. Usually treat with pacemaker.

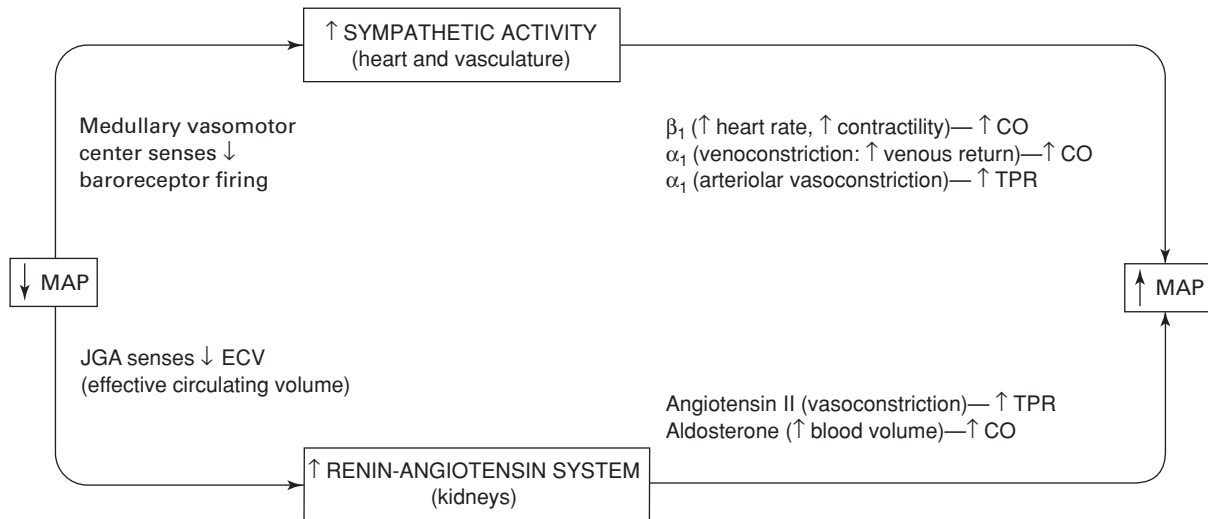


Ventricular fibrillation A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.

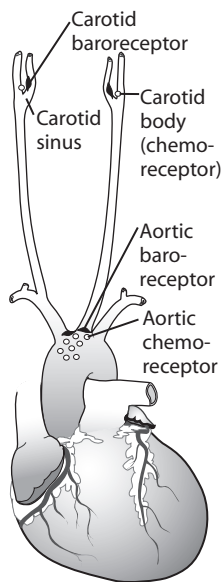


(Adapted, with permission, from Hurst JW. *Introduction to Electrocardiography*. New York: McGraw-Hill, 2001.)

Control of mean arterial pressure



Baroreceptors and chemoreceptors



Receptors:

1. Aortic arch transmits via vagus nerve to medulla (responds only to ↑ blood pressure)
2. Carotid sinus transmits via glossopharyngeal nerve to medulla

Baroreceptors:

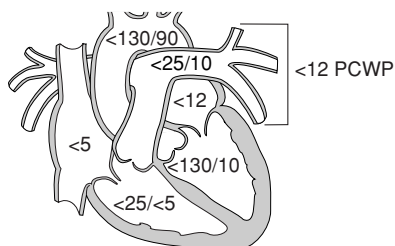
1. Hypotension: ↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
2. Carotid massage: ↑ pressure on carotid artery → ↑ stretch → ↓ HR.

Chemoreceptors:

1. Peripheral: Carotid and aortic bodies respond to ↓ PO_2 (< 60 mmHg), ↑ PCO_2 , and ↓ pH of blood.
2. Central: Respond to changes in pH and PCO_2 of brain interstitial fluid, which in turn are influenced by arterial CO_2 . Do not directly respond to PO_2 . Responsible for Cushing reaction, response to cerebral ischemia, response to ↑ intracranial pressure → hypertension (sympathetic response) and bradycardia (parasympathetic response).

Circulation through organs

Liver	Largest share of systemic cardiac output.
Kidney	Highest blood flow per gram of tissue.
Heart	Large arteriovenous O_2 difference. ↑ O_2 demand is met by ↑ coronary blood flow, not by ↑ extraction of O_2 .

Normal pressures

PCWP—pulmonary capillary wedge pressure (in mmHg) is a good approximation of left atrial pressure. Measured with Swan-Ganz catheter.

Autoregulation**Organ**

Heart

Brain

Kidneys

Lungs

Skeletal muscle

Skin

Mechanism—blood flow is altered to meet demands of tissue.

Factors determining autoregulation

Local metabolites: O_2 , adenosine, NO

Local metabolites: CO_2 (pH)

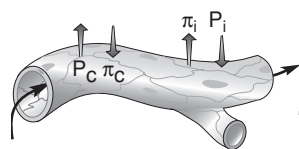
Myogenic and tubuloglomerular feedback

Hypoxia causes vasoconstriction

Local metabolites: lactate, adenosine, K^+

Sympathetic stimulation most important mechanism—temperature control

Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction (in other organs hypoxia causes vasodilation).

Capillary fluid exchange

Starling forces determine fluid movement by osmosis through capillary membranes:

1. P_c = capillary pressure—moves fluid out of capillary
2. P_i = interstitial fluid pressure—moves fluid into capillary
3. π_c = plasma colloid osmotic pressure—moves fluid into capillary
4. π_i = interstitial fluid colloid osmotic pressure—moves fluid out of capillary

Thus, net filtration pressure = $P_{net} = [(P_c - P_i) - (\pi_c - \pi_i)]$.

K_f = filtration constant (capillary permeability).

Net fluid flow = $(P_{net}) (K_f)$.

Edema—excess fluid outflow into interstitium commonly caused by:

1. \uparrow capillary pressure ($\uparrow P_c$; heart failure)
2. \downarrow plasma proteins ($\downarrow \pi_c$; nephrotic syndrome, liver failure)
3. \uparrow capillary permeability ($\uparrow K_f$; toxins, infections, burns)
4. \uparrow interstitial fluid colloid osmotic pressure ($\uparrow \pi_i$; lymphatic blockage)

Common congenital malformations

1. Heart defects
2. Hypospadias
3. Cleft lip (with or without cleft palate)
4. Congenital hip dislocation
5. Spina bifida
6. Anencephaly
7. Pyloric stenosis

Associated with projectile vomiting.

Congenital heart disease

Right-to-left shunts
(early cyanosis)—
“blue babies”

1. Tetralogy of Fallot (most common cause of early cyanosis)
2. Transposition of great vessels
3. Truncus arteriosus

The 3 T's:

Tetralogy
Transposition
Truncus

Children may squat to
↑ venous return.

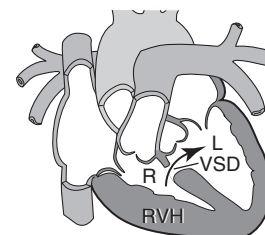
Left-to-right shunts
(late cyanosis)—
“blue kids”

1. VSD (most common congenital cardiac anomaly)
2. ASD (loud S1; wide, fixed split S2)
3. PDA (close with indomethacin)

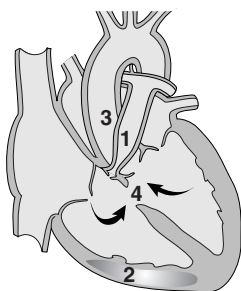
Frequency—VSD > ASD > PDA.
↑ pulmonary resistance due
to arteriolar thickening.
→ progressive pulmonary
hypertension; R → L shunt
(Eisenmenger's).

Eisenmenger's syndrome

Uncorrected VSD, ASD, or PDA leads to progressive pulmonary hypertension. As pulmonary resistance ↑, the shunt reverses from L → R to R → L, which causes late cyanosis (clubbing and polycythemia).



Tetralogy of Fallot



1. Pulmonary stenosis (most important determinant for prognosis)
2. RVH
3. Overriding aorta (overrides the VSD)
4. VSD

Early cyanosis is caused by a right-to-left shunt across the VSD. On x-ray, boot-shaped heart due to RVH. Patients suffer “cyanotic spells.” Tetralogy of Fallot is caused by anterosuperior displacement of the infundibular septum.

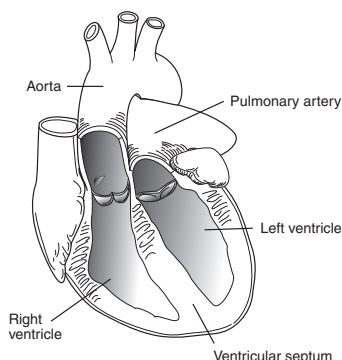
PROVe.

(Adapted, with permission, from Chandrasoma P. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1997:345.)

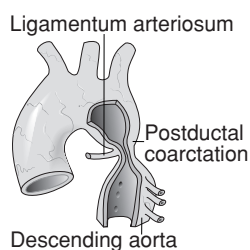
Transposition of great vessels

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow adequate mixing of blood (e.g., VSD, PDA, or patent foramen ovale).

Due to failure of the aortopulmonary septum to spiral. Without surgical correction, most infants die within the first few months of life.

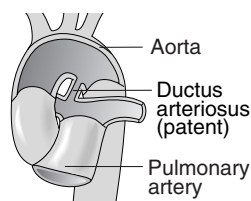


(Adapted, with permission, from Way LW (ed). *Current Surgical Diagnosis and Treatment*, 10th ed. Stamford, CT: Appleton & Lange, 1994:405.)

Coarctation of aorta

Infantile type—aortic stenosis proximal to insertion of ductus arteriosus (preductal).
Adult type—stenosis is distal to ductus arteriosus (postductal). Associated with notching of the ribs, hypertension in upper extremities, weak pulses in lower extremities.

Male-to-female ratio 3:1. Check femoral pulses on physical exam.
INfantile: **IN** close to the heart.
ADult: **D**istal to **D**uctus.

Patent ductus arteriosus

In fetal period, shunt is right to left (normal). In neonatal period, lung resistance ↓ and shunt becomes left to right with subsequent RVH and failure (abnormal). Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O₂ tension.

Indomethacin is used to close a PDA. PGE is used to keep a PDA open, which may be necessary to sustain life in conditions such as transposition of the great vessels.

Congenital cardiac defect associations

Disorder
22q11 syndromes

Down syndrome
Congenital rubella
Turner’s syndrome
Marfan’s syndrome
Offspring of diabetic mother

Defect
Truncus arteriosus, tetralogy of Fallot
ASD, VSD
Septal defects, PDA
Coarctation of aorta
Aortic insufficiency
Transposition of great vessels

Hypertension	Defined as BP \geq 140/90.
Risk factors	\uparrow age, obesity, diabetes, smoking, genetics, black > white > Asian.
Features	90% of hypertension is 1° (essential) and related to \uparrow CO or \uparrow TPR; remaining 10% mostly 2° to renal disease. Malignant hypertension is severe and rapidly progressing.
Predisposes to	Atherosclerosis, stroke, CHF, renal failure, retinopathy, and aortic dissection.

Hyperlipidemia signs

Atheromata	Plaques in blood vessel walls.
Xanthoma	Plaques or nodules composed of lipid-laden histiocytes in the skin, especially the eyelids.
Tendinous xanthoma	Lipid deposit in tendon, especially Achilles.
Corneal arcus	Lipid deposit in cornea, nonspecific (arcus senilis).

Arteriosclerosis

Mönckeberg	Calcification of the arteries, especially radial or ulnar. Usually benign.
Arteriolosclerosis	Hyaline thickening of small arteries in essential hypertension. Hyperplastic “onion skinning” in malignant hypertension.
Atherosclerosis	Fibrous plaques and atheromas form in intima of arteries.

Atherosclerosis

	Disease of elastic arteries and large and medium-sized muscular arteries (see Color Image 79).
Risk factors	Smoking, hypertension, diabetes mellitus, hyperlipidemia, family history.
Progression	Fatty streaks \rightarrow proliferative plaque \rightarrow complex atheromas.
Complications	Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.
Location	Abdominal aorta > coronary artery > popliteal artery > carotid artery.
Symptoms	Angina, claudication, but can be asymptomatic.

Ischemic heart disease

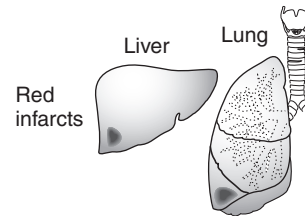
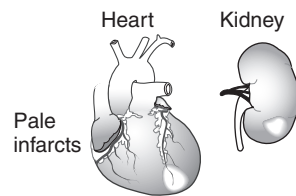
- Possible manifestations:
1. **Angina** (CAD narrowing > 75%):
 - a. Stable—mostly 2° to atherosclerosis (retrosternal chest pain with exertion)
 - b. Prinzmetal’s variant—occurs at rest 2° to coronary artery spasm
 - c. Unstable/crescendo—thrombosis but no necrosis (worsening chest pain)
 2. **Myocardial infarction**—most often acute thrombosis due to coronary artery atherosclerosis. Results in myocyte necrosis.
 3. **Sudden cardiac death**—death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia
 4. **Chronic ischemic heart disease**—progressive onset of CHF over many years due to chronic ischemic myocardial damage

**Infarcts:
red vs. pale**

Red (hemorrhagic) infarcts occur in loose tissues with collaterals, such as lungs, intestine, or following reperfusion.

Pale infarcts occur in solid tissues with single blood supply, such as brain, heart, kidney, and spleen.

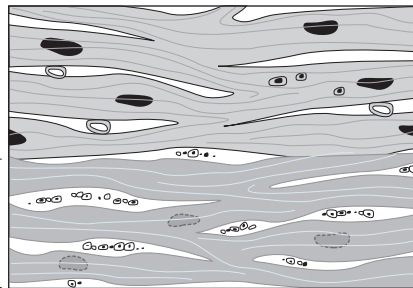
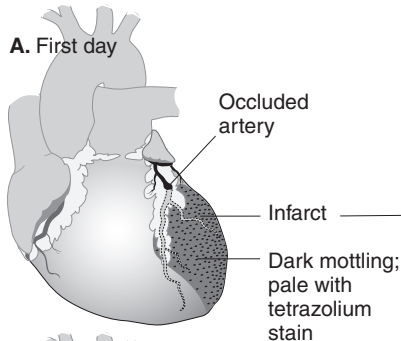
REd = REperfusion.



Evolution of MI

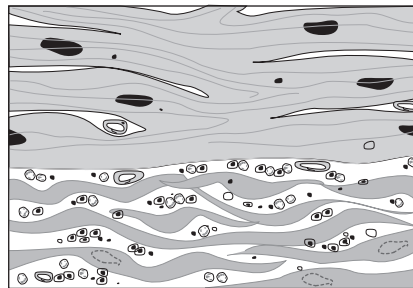
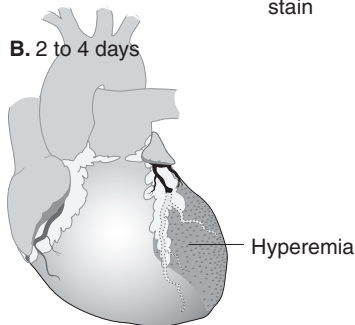
Coronary artery occlusion: LAD > RCA > circumflex.

Symptoms: Diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue, adrenergic symptoms (see Color Image 80).



No visible change by light microscopy in first 2–4 hours.

Coagulative necrosis; contraction bands visible after 4 hours. Release of contents of necrotic cells into bloodstream and the beginning of neutrophil emigration

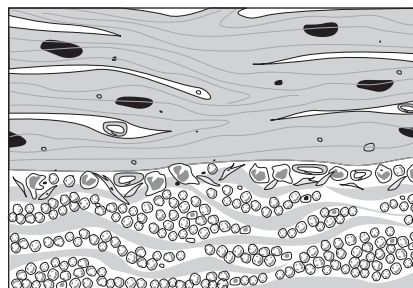
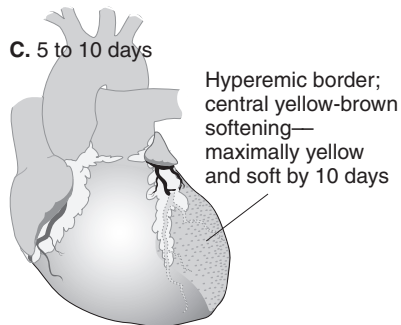


Tissue surrounding infarct shows acute inflammation

Dilated vessels (hyperemia)

Neutrophil emigration

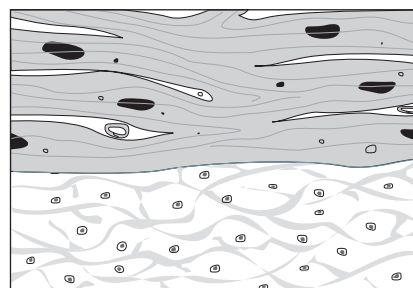
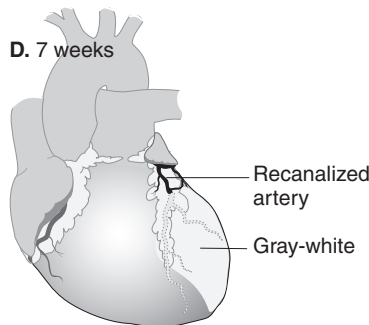
Muscle shows extensive coagulative necrosis



Outer zone (ingrowth of granulation tissue)

Macrophages

Neutrophils



Contracted scar complete

(Adapted, with permission, from Chandrasoma P. *Pathology Notes*. Stamford, CT: Appleton & Lange, 1991:244.)

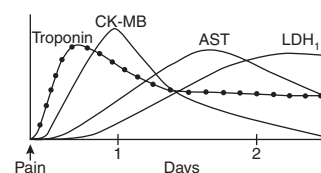
Diagnosis of MI

In the first 6 hours, ECG is the gold standard.
Cardiac troponin I rises after 4 hours and is elevated for 7–10 days; more specific than other protein markers.

CK-MB is predominantly found in myocardium but can also be released from skeletal muscle.

AST is nonspecific and can be found in cardiac, liver, and skeletal muscle cells.

ECG changes can include ST elevation (transmural infarct), ST depression (subendocardial infarct), and pathological Q waves (transmural infarct).

**MI complications**

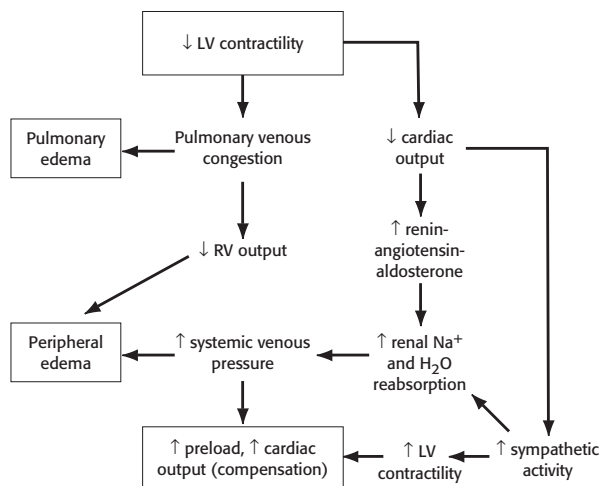
1. Cardiac arrhythmia—important cause of death before reaching hospital; common in first few days
2. LV failure and pulmonary edema
3. Cardiogenic shock (large infarct—high risk of mortality)
4. Rupture of ventricular free wall, interventricular septum, papillary muscle (4–10 days post-MI), cardiac tamponade
5. Aneurysm formation—↓ CO, risk of arrhythmia, embolus from mural thrombus
6. Fibrinous pericarditis—friction rub (3–5 days post-MI)
7. Dressler's syndrome—autoimmune phenomenon resulting in fibrinous pericarditis (several weeks post-MI)

Cardiomyopathies

Dilated (congestive) cardiomyopathy	Most common cardiomyopathy (90% of cases). Etiologies include chronic Alcohol abuse, Beriberi, Coxsackie B virus myocarditis, chronic Cocaine use, Chagas' disease, Doxorubicin toxicity, peripartum cardiomyopathy, and hemochromatosis. Heart dilates and looks like a balloon on chest x-ray.	Systolic dysfunction ensues.
Hypertrophic cardiomyopathy	Hypertrophy often asymmetric and involving the intraventricular septum. 50% of cases are familial, autosomal dominant. Cause of sudden death in young athletes. Findings: loud S4, apical impulses, systolic murmur. Treat with β -blocker.	Diastolic dysfunction ensues.
Restrictive/obliterative cardiomyopathy	Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis, and endomyocardial fibrosis (Löffler's).	

CHF

Abnormality	Cause
Dyspnea on exertion	Failure of LV output to \uparrow during exercise.
Cardiac dilation	Greater ventricular end-diastolic volume.
Pulmonary edema, paroxysmal nocturnal dyspnea	LV failure \rightarrow \uparrow pulmonary venous pressure \rightarrow pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages ("heart failure" cells).
Orthopnea (shortness of breath when supine)	\uparrow venous return in supine position exacerbates pulmonary vascular congestion.
Hepatomegaly (nutmeg liver)	\uparrow central venous pressure \rightarrow \uparrow resistance to portal flow. Rarely, leads to "cardiac cirrhosis."
Ankle, sacral edema	RV failure \rightarrow \uparrow venous pressure \rightarrow fluid transudation.

**Embolus types**

Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. Fat emboli are associated with long bone fractures and liposuction. Amniotic fluid emboli can lead to DIC, especially postpartum. Pulmonary embolus—chest pain, tachypnea, dyspnea.

An embolus moves like a **FAT BAT**. Approximately 95% of pulmonary emboli arise from deep leg veins.

Deep venous thrombosis

Predisposed by Virchow's triad:

1. Stasis
2. Hypercoagulability
3. Endothelial damage

Cardiac tamponade

Compression of heart by fluid (i.e., blood) in pericardium, leading to \downarrow CO. Equilibration of pressures in all 4 chambers. Findings: hypotension, \uparrow venous pressure (JVD), distant heart sounds. Pulsus paradoxus; ECG shows electrical alternans (beat-to-beat alterations of QRS complex height).

Bacterial endocarditis

New murmur, anemia, fever, Osler's nodes (tender raised lesions on finger or toe pads), Roth's spots (round white spots on retina surrounded by hemorrhage), Janeway lesions (small erythematous lesions on palm or sole), splinter hemorrhages on nail bed. Valvular damage may cause new murmur. Multiple blood cultures necessary for diagnosis (see Color Image 82).

1. Acute—*S. aureus* (high virulence). Large vegetations on previously normal valves. Rapid onset.
2. Subacute—viridans streptococcus (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. More insidious onset.

Endocarditis may also be nonbacterial 2° to metastasis or renal failure (marantic/thrombotic endocarditis).

Mitral valve is most frequently involved. Tricuspid valve endocarditis is associated with IV drug abuse.

Complications:
chordae rupture,
glomerulonephritis,
suppurative pericarditis,
emboli.

Bacteria FROM JANE:

Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhage
Emboli

Libman-Sacks endocarditis

Vegetations develop on both sides of valve (→ mitral valve stenosis) but do not embolize. Seen in lupus.

SLE causes **LSE**.

Rheumatic heart disease

Rheumatic fever is a consequence of pharyngeal infection with group A β -hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Associated with Aschoff bodies, migratory polyarthritis, erythema marginatum, elevated ASO titers.

Immune mediated, not direct effect of bacteria (see Color Image 85).

FEVERSS:

Fever
Erythema marginatum
Valvular damage
ESR ↑
Red-hot joints (polyarthritis)
Subcutaneous nodules
St. Vitus' dance (chorea)

Aschoff body

Aschoff bodies (granuloma with giant cells) and Anitschkow's cells (activated histiocytes) are found in rheumatic heart disease.

Think of two **RH**ussians with **RH**eumatic heart disease (Aschoff and Anitschkow).

Pericarditis

Serous
Fibrinous
Hemorrhagic

Caused by SLE, rheumatoid arthritis, infection, uremia.

Uremia, MI, rheumatic fever.

TB, malignancy (e.g., melanoma).

Findings: pericardial pain, friction rub, ECG changes (diffuse ST elevations in all leads), pulsus paradoxus, distant heart sounds.

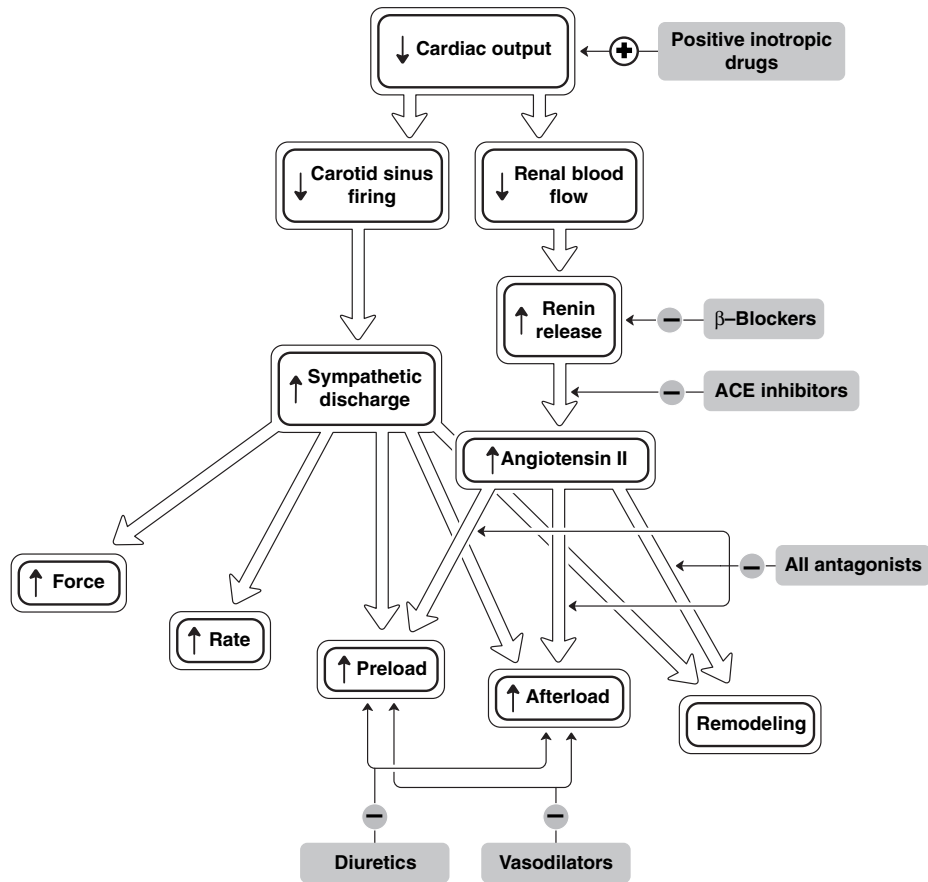
Can resolve without scarring or lead to chronic adhesive or chronic constrictive pericarditis.

Syphilitic heart disease

3° syphilis disrupts the vasa vasora of the aorta with consequent dilation of the aorta and valve ring. Often affects the aortic root and calcification of ascending arch of the aorta.
May see calcification of the aortic root and ascending aortic arch.

Can result in aneurysm of the ascending aorta or aortic arch and aortic valve incompetence.

Cardiovascular therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:39.)

Antihypertensive drugs

Drug	Adverse effects
Diuretics	
Hydrochlorothiazide	Hypokalemia, slight hyperlipidemia, hyperuricemia, lassitude, hypercalcemia, hyperglycemia
Loop diuretics	Potassium wasting, metabolic alkalosis, hypotension, ototoxicity
Sympathoplegics	
Clonidine	Dry mouth, sedation, severe rebound hypertension
Methyldopa	Sedation, positive Coombs' test
Hexamethonium	Severe orthostatic hypotension, blurred vision, constipation, sexual dysfunction
Reserpine	Sedation, depression, nasal stuffiness, diarrhea
Guanethidine	Orthostatic and exercise hypotension, sexual dysfunction, diarrhea
Prazosin	1st-dose orthostatic hypotension, dizziness, headache
β -blockers	Impotence, asthma, cardiovascular effects (bradycardia, CHF, AV block), CNS effects (sedation, sleep alterations)
Vasodilators	
Hydralazine ^a	Nausea, headache, lupus-like syndrome, reflex tachycardia, angina, salt retention
Minoxidil ^a	Hypertrichosis, pericardial effusion, reflex tachycardia, angina, salt retention
Nifedipine, verapamil	Dizziness, flushing, constipation (verapamil), nausea
Nitroprusside	Cyanide toxicity (releases CN)
ACE inhibitors	
Captopril	Hyperkalemia, Cough, Angioedema, Proteinuria, Taste changes, hypotension, Pregnancy problems (fetal renal damage), Rash, Increased renin, Lower angiotensin II
Angiotensin II receptor inhibitors	
Losartan	Fetal renal toxicity, hyperkalemia

^aUse with β -blockers to prevent reflex tachycardia, diuretic to block salt retention.

Hydralazine

Mechanism	\uparrow cGMP \rightarrow smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
Clinical use	Severe hypertension, CHF.
Toxicity	Compensatory tachycardia, fluid retention. Lupus-like syndrome.

Calcium channel blockers

Mechanism	Nifedipine, verapamil, diltiazem. Block voltage-dependent L-type calcium channels of cardiac and smooth muscle and thereby reduce muscle contractility. Vascular smooth muscle—nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > nifedipine.
Clinical use	Hypertension, angina, arrhythmias (not nifedipine).
Toxicity	Cardiac depression, peripheral edema, flushing, dizziness, and constipation.

Nitroglycerin, isosorbide dinitrate

Mechanism	Vasodilate by releasing nitric oxide in smooth muscle, causing ↑ in cGMP and smooth muscle relaxation. Dilate veins >> arteries. ↓ preload.
Clinical use	Angina, pulmonary edema. Also used as an aphrodisiac and erection enhancer.
Toxicity	Tachycardia, hypotension, headache, “Monday disease” in industrial exposure, development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend, resulting in tachycardia, dizziness, and headache.

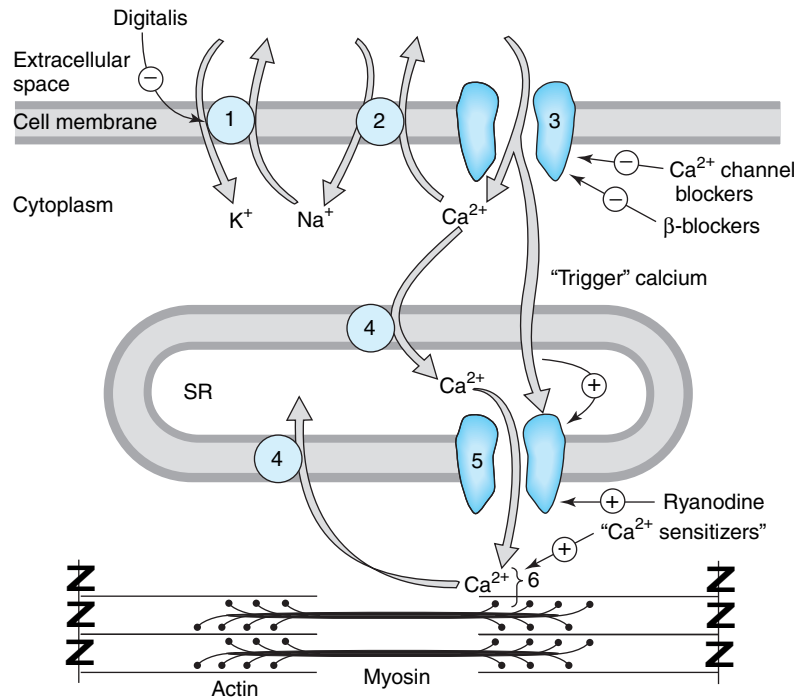
Antianginal therapy

Goal—reduction of myocardial O₂ consumption (MVO₂) by decreasing 1 or more of the determinants of MVO₂: end diastolic volume, blood pressure, heart rate, contractility, ejection time.

Component	Nitrates (affect preload)	β-blockers (affect afterload)	Nitrates + β-blockers
End diastolic volume	↓	↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	↓
Ejection time	↓	↑	Little/no effect
MVO ₂	↓	↓	↓↓

Calcium channel blockers—Nifedipine is similar to Nitrates in effect; verapamil is similar to β-blockers in effect.

Cardiac drugs: sites of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1998:198.)

Cardiac sarcomere is shown above with the cellular components involved in excitation-contraction coupling. Factors involved in excitation-contraction coupling are numbered. (1) Na^+/K^+ ATPase; (2) $\text{Na}^+-\text{Ca}^{2+}$ exchanger; (3) voltage-gated calcium channel; (4) calcium pump in the wall of the sarcoplasmic reticulum (SR); (5) calcium release channel in the SR; (6) site of calcium interaction with troponin-tropomyosin system.

Cardiac glycosides

Mechanism

Digoxin—75% bioavailability, 20–40% protein bound, $t_{1/2} = 40$ hours, urinary excretion. Inhibit the Na^+/K^+ ATPase of cell membrane, causing \uparrow intracellular Na^+ . $\text{Na}^+-\text{Ca}^{2+}$ antiport does not function as efficiently, causing \uparrow intracellular Ca^{2+} ; leads to positive inotropy. May cause \uparrow PR, \downarrow QT, scooping of ST segment, T-wave inversion on ECG. CHF (\uparrow contractility); atrial fibrillation (\downarrow conduction at AV node).

Clinical use

Toxicity

Nausea, vomiting, diarrhea. Blurry yellow vision (think Van Gogh). Arrhythmia. Toxicities of digoxin are \uparrow by renal failure (\downarrow excretion), hypokalemia (potentiates drug's effects), and quinidine (\downarrow digoxin clearance; displaces digoxin from tissue binding sites).

Antidote

Slowly normalize K^+ , lidocaine, cardiac pacer, anti-dig Fab fragments.

**Antiarrhythmics—
Na⁺ channel
blockers (class I)**

Local anesthetics. Slow or block (↓) conduction (especially in depolarized cells).
↓ slope of phase 4 depolarization and ↑ threshold for firing in abnormal pacemaker cells. Are state dependent (selectively depress tissue that is frequently depolarized, e.g., fast tachycardia).

Class IA

Quinidine, **A**miodarone, **P**rocainamide, **D**isopyramide.
↑ AP duration, ↑ effective refractory period (ERP),
↑ QT interval. Affect both atrial and ventricular
arrhythmias.

**“Queen Amy Proclaims
Diso’s pyramid.”**

Toxicity: quinidine (cinchonism—headache, tinnitus;
thrombocytopenia; torsades de pointes due to ↑
QT interval); procainamide (reversible SLE-like
syndrome).

Class IB

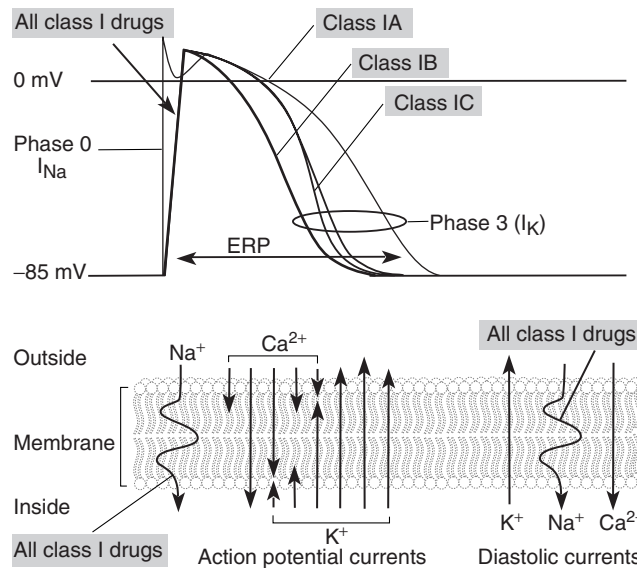
Lidocaine, mexiletine, tocainide. ↓ AP duration.
Affect ischemic or depolarized Purkinje and
ventricular tissue. Useful in acute ventricular
arrhythmias (especially post-MI) and in
digitalis-induced arrhythmias.

Toxicity: local anesthetic. CNS stimulation/depression,
cardiovascular depression.

Class IC

Flecainide, encainide, propafenone. No effect on
AP duration. Useful in V-tachs that progress to VF
and in intractable SVT. Usually used only as last
resort in refractory tachyarrhythmias.

Toxicity: proarrhythmic, especially post-MI
(contraindicated).



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:118.)

**Antiarrhythmics—
β-blockers
(class II)**

Propranolol, esmolol, metoprolol, atenolol, timolol.

Mechanism

↓ cAMP, ↓ Ca^{2+} currents. Suppress abnormal pacemakers by ↓ slope of phase 4.
AV node particularly sensitive—↑ PR interval. Esmolol very short acting.

Toxicity

Impotence, exacerbation of asthma, cardiovascular effects (bradycardia, AV block, CHF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia.

**Antiarrhythmics—
 K^+ channel
blockers (class III)**

Sotalol, ibutilide, bretylium, amiodarone.

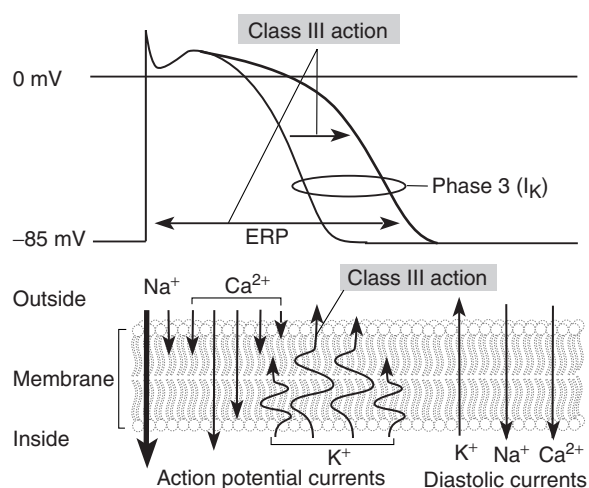
Mechanism

↑ AP duration, ↑ ERP. Used when other antiarrhythmics fail. ↑ QT interval.

Toxicity

Sotalol—torsades de pointes, excessive β block;
ibutilide—torsades; bretylium—new arrhythmias, hypotension; amiodarone—**pulmonary fibrosis**, corneal deposits, **hepatotoxicity**, skin deposits resulting in photodermatitis, neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, CHF), **hypothyroidism/hyperthyroidism**.

Remember to check **PFTs**, **LFTs**, and **TFTs** when using amiodarone.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:120.)

**Antiarrhythmics—
Ca²⁺ channel
blockers (class IV)**

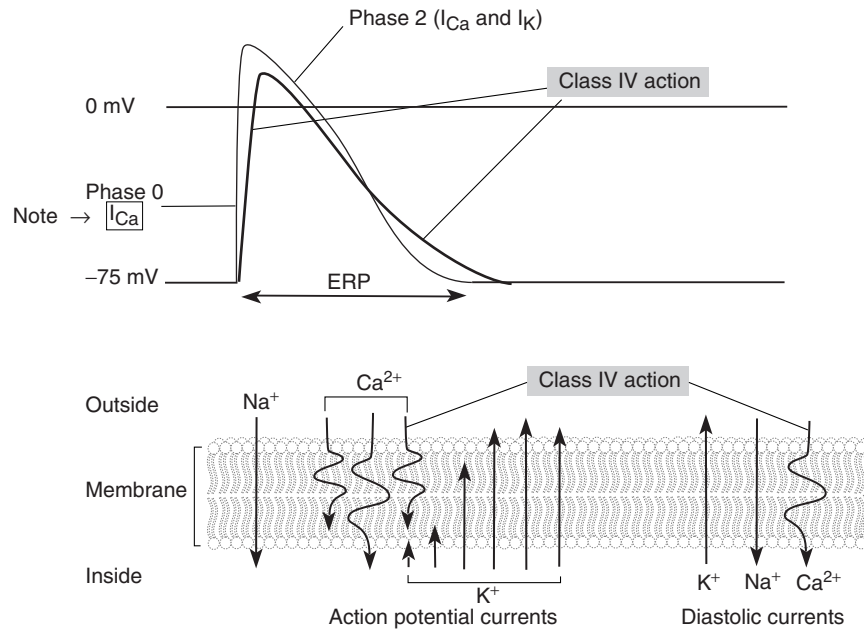
Mechanism

Toxicity

Verapamil, diltiazem.

Primarily affect AV nodal cells. ↓ conduction velocity, ↑ ERP, ↑ PR interval. Used in prevention of nodal arrhythmias (e.g., SVT).

Constipation, flushing, edema, CV effects (CHF, AV block, sinus node depression); torsades de pointes (bepridil).



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:121.)

Other antiarrhythmics

Adenosine

K⁺

Mg⁺

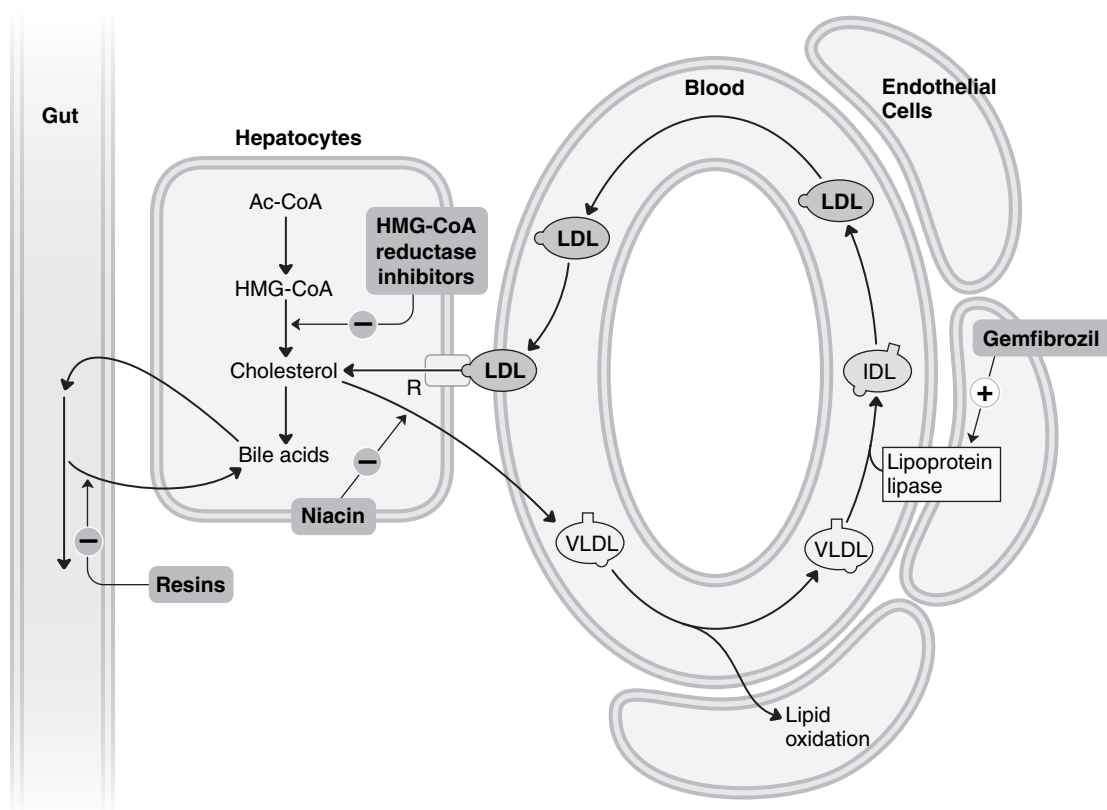
Drug of choice in diagnosing/abolishing AV nodal arrhythmias.

Depresses ectopic pacemakers, especially in digoxin toxicity.

Effective in torsades de pointes and digoxin toxicity.

Lipid-lowering agents

Drug	Effect on LDL “bad cholesterol”	Effect on HDL “good cholesterol”	Effect on triglycerides	Side effects/problems
HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin, atorvastatin)	↓↓↓	↑	↓	Expensive, reversible ↑ LFTs, myositis
Niacin	↓↓	↑↑	↓	Red, flushed face, which is ↓ by aspirin or long-term use
Bile acid resins (cholestyramine, colestipol)	↓↓	—	Slightly ↑	Patients hate it—tastes bad and causes GI discomfort
Cholesterol absorption blocker (ezetimibe)	↓↓	—	—	Rare ↑ LFTs
“Fibrates” (gemfibrozil, clofibrate, bezafibrate, fenofibrate)	↓	↑	↓↓↓	Myositis, ↑ LFTs



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:56.)

Endocrine

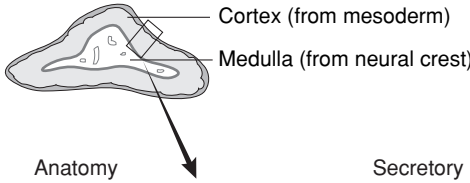
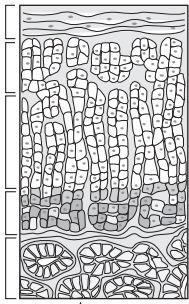
“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”

—Elaine Sherman, *Book of Divine Indulgences*

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

■ Woman presents with diffuse goiter and hyperthyroidism.	What are the expected values of TSH and thyroid hormones?	Low TSH and high thyroid hormones.
■ 48-year-old female presents with progressive lethargy and extreme sensitivity to cold temperatures.	What is the diagnosis?	Hypothyroidism.
■ Patient with elevated serum cortisol levels undergoes a dexamethasone suppression test. 1 mg of dexamethasone does not ↓ cortisol levels, but 8 mg does.	What is the diagnosis?	Pituitary tumor.
■ 50-year-old man complains of diarrhea. On physical exam, his face is plethoric and a heart murmur is detected.	What is the diagnosis?	Carcinoid syndrome.
■ Woman of short stature presents with shortened 4th and 5th metacarpals.	What endocrine disorder comes to mind?	Albright's hereditary osteodystrophy, or pseudohypoparathyroidism.
■ Nondiabetic patient presents with hypoglycemia but low levels of C peptide.	What is the diagnosis?	Surreptitious insulin injection.

Adrenal cortex and medulla

			
Primary regulatory control	Anatomy	Secretory products	
	Capsule		
Renin-angiotensin	→ Zona Glomerulosa	→ Aldosterone	
ACTH, hypothalamic CRH	→ Zona Fasciculata	→ Cortisol, sex hormones	
ACTH, hypothalamic CRH	→ Zona Reticularis	→ Sex hormones (e.g., androgens)	
Preganglionic sympathetic fibers	→ Medulla	→ Catecholamines (Epi, NE)	
	Chromaffin cells →		
<hr/>			
Adrenal gland drainage	Left adrenal → left adrenal vein → left renal vein → IVC. Right adrenal → right adrenal vein → IVC.		
<hr/>			
Pituitary gland	Posterior pituitary → vasopressin and oxytocin, made in the hypothalamus and shipped to pituitary. Derived from neuroectoderm. Anterior pituitary → FSH, LH, ACTH, GH, TSH, melanotropin (MSH), prolactin. Derived from oral ectoderm. α subunit—common subunit to TSH, LH, FSH, and hCG. β subunit—determines hormone specificity.	Acidophils—GH, prolactin. FLAT PiG: FSH LH ACTH TSH Prolactin GH	
<hr/>			
Endocrine pancreas cell types	Islets of Langerhans are collections of α , β , and δ endocrine cells (most numerous in tail of pancreas). Islets arise from pancreatic buds. α = glucagon; β = insulin; δ = somatostatin.		

GFR corresponds with Salt (Na^+), Sugar (glucocorticoids), and Sex (androgens).

“The deeper you go, the sweeter it gets.”

Pheochromocytoma—most common tumor of the adrenal medulla in adults.

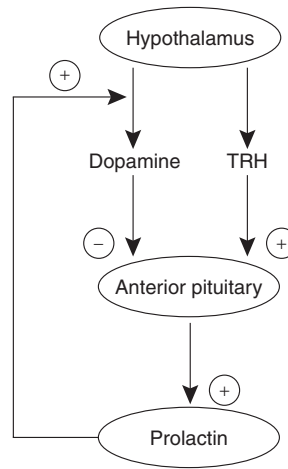
Neuroblastoma—most common in children.

Pheochromocytoma causes episodic hypertension; neuroblastoma does not.

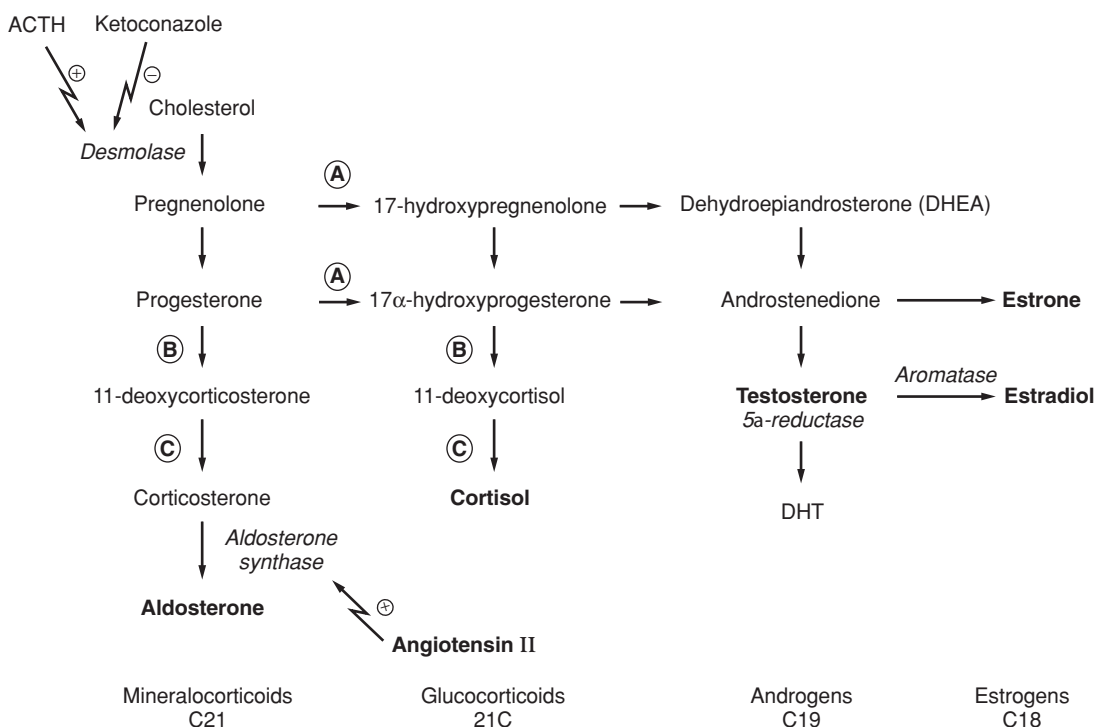
Prolactin regulation

Prolactin \uparrow dopamine synthesis and secretion from the hypothalamus. Dopamine subsequently **inhibits** prolactin secretion. Dopamine agonists (e.g., bromocriptine) therefore **inhibit** prolactin secretion, whereas dopamine antagonists (e.g., most antipsychotics) stimulate prolactin secretion. In females, prolactin inhibits GnRH synthesis and release, which inhibits ovulation. Amenorrhea is commonly seen in prolactinomas.

Prolactin regulation



Adrenal steroids



Congenital
adrenal
hyperplasias

- A = 17 α -hydroxylase deficiency.** ↓ sex hormones, ↓ cortisol, ↑ mineralocorticoids. Cx = **HYPER**tension, hypokalemia; phenotypically female but no maturation.
- B = 21 β -hydroxylase deficiency.** Most common form. ↓ cortisol (increased ACTH), ↓ mineralocorticoids, ↑ sex hormones. Cx = masculinization, female pseudohermaphroditism, **HYPO**tension, hyponatremia, hyperkalemia, ↑ plasma renin activity, and volume depletion. Salt wasting can lead to hypovolemic shock in the newborn.
- C = 11 β -hydroxylase deficiency.** ↓ cortisol, ↓ aldosterone and corticosterone, ↑ sex hormones. Cx = masculinization, **HYPER**tension (11-deoxycorticosterone acts as a weak mineralocorticoid).

PTH

Source

Chief cells of parathyroid.

Function

1. ↑ bone resorption of calcium and phosphate
2. ↑ kidney reabsorption of calcium in distal convoluted tubule
3. ↓ kidney reabsorption of phosphate
4. ↑ 1,25-(OH)₂ vitamin D (cholecalciferol) production by stimulating kidney 1α-hydroxylase

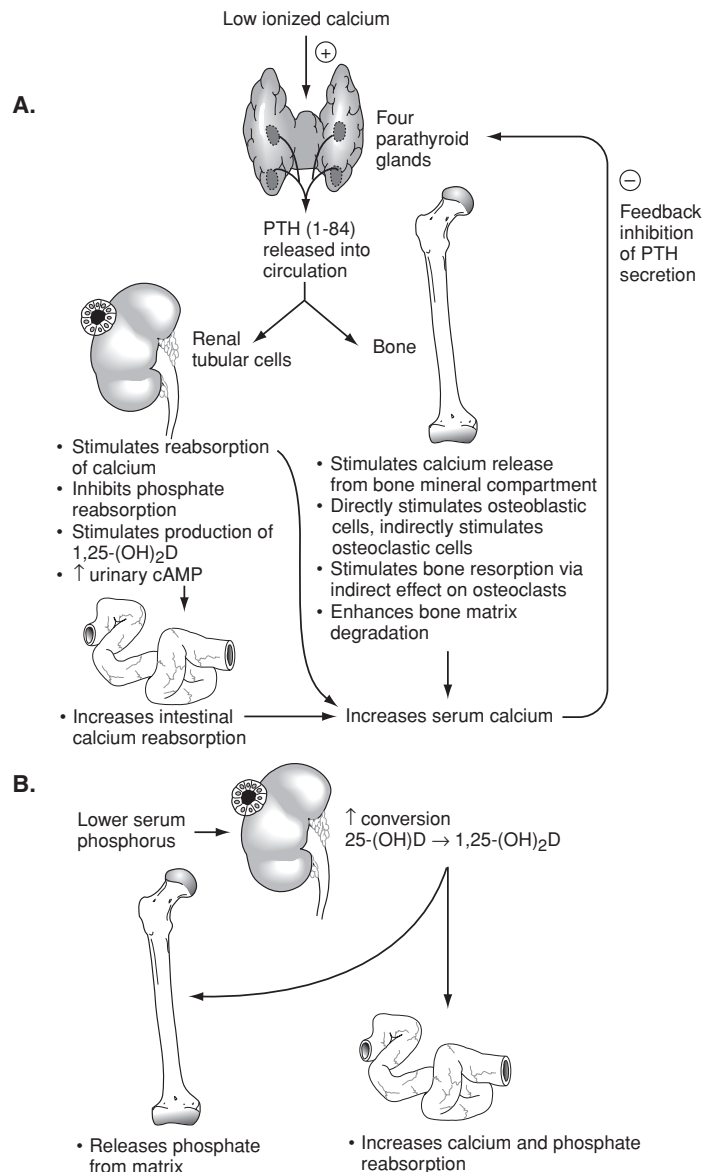
PTH ↑ serum Ca²⁺, ↓ serum (PO₄)³⁻, ↑ urine (PO₄)³⁻.

PTH stimulates both osteoclasts and osteoblasts.

PTH = Phosphate Trashing Hormone.

Regulation

↓ in free serum Ca²⁺ ↑ PTH secretion.



(Adapted, with permission, from Chandrasoma P et al. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998.)

Shown above are the main actions of PTH and 1,25-(OH)₂D in the maintenance of calcium (A) and phosphate (B) homeostasis.

Vitamin D

Source	Vitamin D ₃ from sun exposure in skin. D ₂ from plants. Both converted to 25-OH vitamin D in liver and to 1,25-(OH) ₂ vitamin D (active form) in kidney.	If you do not get vitamin D, you get rickets (kids) or osteomalacia (adults). 24,25-(OH) ₂ vitamin D is an inactive form of vitamin D.
Function	1. ↑ absorption of dietary calcium 2. ↑ absorption of dietary phosphate 3. ↑ bone resorption of Ca ²⁺ and (PO ₄) ³⁻	
Regulation	↑ PTH causes ↑ 1,25-(OH) ₂ vitamin D formation. ↓ [Ca ²⁺] ↑ 1,25-(OH) ₂ vitamin D production. ↓ phosphate causes ↑ 1,25-(OH) ₂ vitamin D conversion. 1,25-(OH) ₂ vitamin D feedback inhibits its own production.	

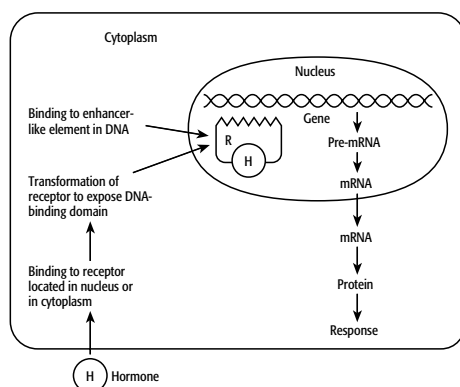
Calcium, phosphate, and alkaline phosphatase levels

	Ca ²⁺	Phosphate	Alkaline phosphatase
Hyperparathyroidism	↑	↓	↑
Paget's disease of bone	N/↑	N	↑↑↑
Vitamin D intoxication	↑	↑	N/↑
Osteoporosis	N	N	N
Renal insufficiency	↓	↑	N

N = no change.

Calcitonin

Source	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. It is probably not important in normal calcium homeostasis.
Function	↓ bone resorption of calcium.	
Regulation	↑ serum Ca ²⁺ causes calcitonin secretion.	

Steroid/thyroid hormone mechanism(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 20th ed. New York: McGraw-Hill, 2001.)

The need for gene transcription and protein synthesis delays the onset of action of these hormones.

Steroid/thyroid hormones—

PET CAT:

Progesterone
Estrogen
Testosterone
Cortisol
Aldosterone
Thyroxine and T₃

Steroid hormones are lipophilic and insoluble in plasma; therefore, they must circulate bound to specific binding globulins, which ↑ solubility and allows for ↑ delivery of steroid to the target organ. ↑ levels of sex hormone-binding globulin (SHBG) lower free testosterone → gynecomastia. ↓ SHBG raises free testosterone → hirsutism.

Thyroid hormones

(T_3/T_4)

Source

Function

Regulation

Iodine-containing hormones that control the body's metabolic rate.

Follicles of thyroid. Most T_3 formed in blood.

1. Bone growth (synergism with GH)
 2. CNS maturation
 3. β -adrenergic effects (\uparrow CO, HR, SV, contractility)
 4. \uparrow basal metabolic rate via \uparrow Na^+/K^+ ATPase activity = \uparrow O_2 consumption, RR, \uparrow body temperature
 5. \uparrow glycogenolysis, gluconeogenesis, lipolysis
- TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. Negative feedback by T_3 to anterior pituitary \downarrow sensitivity to TRH. TSI, like TSH, stimulates follicular cells (Graves' disease).

T_3 functions—4 B's:

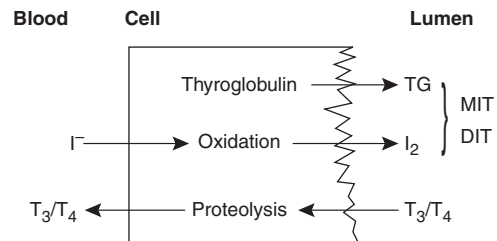
Brain maturation

Bone growth

Beta-adrenergic effects

BMR \uparrow

Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active. \downarrow TBG in hepatic failure; \uparrow TBG in pregnancy.



Insulin-dependent organs

Skeletal muscle and adipose tissue depend on insulin for \uparrow glucose uptake. Brain and RBCs take up glucose independent of insulin levels (GLUT-1).

Brain and RBCs depend on glucose for metabolism under normal circumstances. Brain uses ketone bodies in starvation.

Cushing's syndrome

↑ cortisol due to a variety of causes.

Etiologies include:

1. Cushing's disease (1° pituitary adenoma); ↑ ACTH
2. 1° adrenal (hyperplasia/neoplasia); ↓ ACTH (see Color Image 68)
3. Ectopic ACTH production (e.g., small cell lung cancer); ↑ ACTH
4. Iatrogenic (e.g., chronic steroids); ↓ ACTH

The clinical picture includes hypertension, weight gain, moon facies, truncal obesity, buffalo hump, hyperglycemia (insulin resistance), skin changes (thinning, striae), osteoporosis, amenorrhea, and immune suppression (see Color Image 70).

Dexamethasone suppression test:

Healthy—↓ cortisol after low dose.

ACTH-producing tumor—
↑ cortisol after low dose;
↓ cortisol after high dose.

Cortisone-producing tumor—↑ cortisol after low and high dose.

Hyperaldosteronism

Primary (Conn's syndrome)

Caused by an aldosterone-secreting tumor, resulting in hypertension, hypokalemia, metabolic alkalosis, and **low** plasma renin.

Treatment includes spironolactone, a K⁺-sparing diuretic that works by acting as an aldosterone antagonist.

Secondary

Due to renal artery stenosis, chronic renal failure, CHF, cirrhosis, or nephrotic syndrome. Kidney perception of low intravascular volume results in an overactive renin-angiotensin system. Therefore, it is associated with **high** plasma renin.

Addison's disease

1° deficiency of aldosterone and cortisol due to adrenal atrophy, causing hypotension (hyponatremic volume contraction) and skin hyperpigmentation (due to MSH, a by-product of ↑ ACTH production from POMC). Characterized by **Adrenal Atrophy** and **Absence** of hormone production; involves **All 3** cortical divisions. Distinguish from 2° insufficiency, which has no skin hyperpigmentation (↓ pituitary ACTH production).

Tumors of the adrenal medulla

Pheochromocytoma

The most common tumor of the adrenal medulla in adults. Derived from chromaffin cells (arise from neural crest) (see Color Image 69).

Pheochromocytomas may be associated with neurofibromatosis, MEN types II and III.

Neuroblastoma

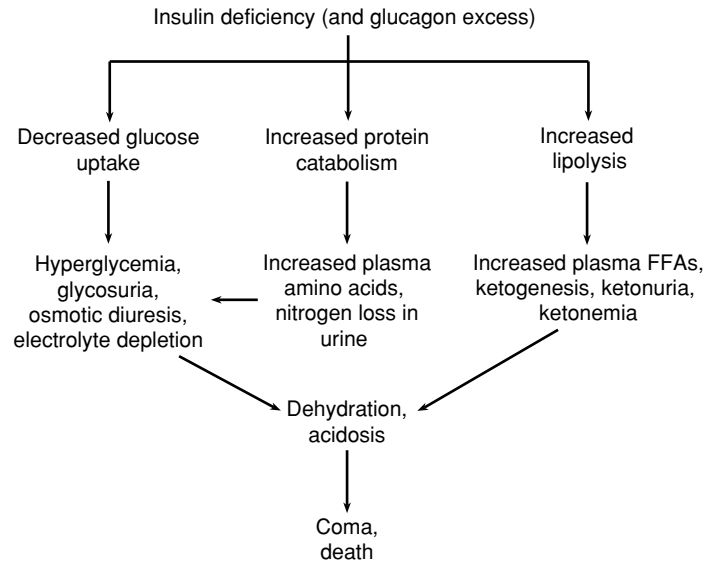
The most common tumor of the adrenal medulla in children, but it can occur anywhere along the sympathetic chain.

Pheochromocytoma	<p>Most of these tumors secrete epinephrine, NE, and dopamine. Urinary VMA levels and plasma catecholamines are elevated. Associated with MEN types II and III. Treated with α-antagonists, especially phenoxybenzamine, a nonselective, irreversible α-blocker.</p> <p>Episodic hyperadrenergic symptoms (5 P's):</p> <ul style="list-style-type: none"> Pressure (elevated blood pressure) Pain (headache) Perspiration (tachycardia) Palpitations Pallor 	<p>Rule of 10's:</p> <ul style="list-style-type: none"> 10% malignant 10% bilateral 10% extra-adrenal 10% calcify 10% kids 10% familial <p>Symptoms occur in “spells”—relapse and remit.</p>
Multiple endocrine neoplasias (MEN)	<p>MEN type I (Wermer's syndrome)—pancreas (e.g., Zollinger-Ellison syndrome, insulinomas, VIPomas), parathyroid, and pituitary tumors. Presents with kidney stones and stomach ulcers.</p> <p>MEN type II (Sipple's syndrome)—medullary carcinoma of the thyroid, pheochromocytoma, parathyroid tumor.</p> <p>MEN type III (formerly MEN IIb)—medullary carcinoma of the thyroid, pheochromocytoma, and oral and intestinal ganglioneuromatosis (mucosal neuromas).</p>	<p>MEN I = 3 “P” organs (Pancreas, Pituitary, and Parathyroid).</p> <p>All MEN syndromes have autosomal-dominant inheritance.</p> <p>Associated with <i>ret</i> gene in MEN types II and III.</p>
Hypothyroidism and hyperthyroidism		
Hypothyroidism	Cold intolerance, hypoactivity, weight gain, fatigue, lethargy, ↓ appetite, constipation, weakness, ↓ reflexes, myxedema (facial/periorbital), dry, cool skin, and coarse, brittle hair.	↑ TSH (sensitive test for 1° hypothyroidism), ↓ total T ₄ , ↓ free T ₄ , ↓ T ₃ uptake.
Hyperthyroidism	Heat intolerance, hyperactivity, weight loss, chest pain/palpitations, arrhythmias, diarrhea, ↑ reflexes, warm, moist skin, and fine hair.	Riedel's thyroiditis—thyroid replaced by fibrous tissue (hypothyroid). ↓ TSH (if 1°), ↑ total T ₄ , ↑ free T ₄ , ↑ T ₃ uptake.
Graves' disease	An autoimmune hyperthyroidism with thyroid-stimulating/TSH receptor antibodies. Ophthalmopathy (proptosis, EOM swelling), pretibial myxedema, diffuse goiter. Often presents during stress (e.g., childbirth) (see Color Image 71).	Graves' is a type II hypersensitivity.
Hashimoto's thyroiditis	Autoimmune disorder resulting in hypothyroidism. Slow course; moderately enlarged, nontender thyroid. Lymphocytic infiltrate with germinal centers. Antimicrosomal and antithyroglobulin antibodies.	
Subacute thyroiditis (de Quervain's)	Self-limited hypothyroidism often following a flulike illness. Elevated ESR, jaw pain, early inflammation, and very tender thyroid gland.	May be hyperthyroid early in course.

Thyroid cancer	<ol style="list-style-type: none"> 1. Papillary carcinoma—most common, excellent prognosis, “ground-glass” nuclei, psammoma bodies. 2. Follicular carcinoma—good prognosis, uniform follicles. 3. Medullary carcinoma—from parafollicular “C cells”; produces calcitonin, sheets of cells in amyloid stroma. MEN types II and III. 4. Undifferentiated/anaplastic—older patients, very poor prognosis. 	
Cretinism	<p>Endemic cretinism occurs wherever endemic goiter is prevalent (lack of dietary iodine); sporadic cretinism is caused by defect in T_4 formation or developmental failure in thyroid formation.</p> <p>Findings: pot-bellied, pale, puffy-faced child with protruding umbilicus and protuberant tongue.</p>	<p>Cretin means Christlike (French <i>chrétien</i>). Those affected were considered so mentally retarded as to be incapable of sinning. Still common in China.</p>
Acromegaly	<p>Excess GH in adults. Findings: large tongue with deep furrows, deep voice, large hands and feet, coarse facial features, impaired glucose tolerance (insulin resistance). \uparrow GH in children \rightarrow gigantism. Treat medically with octreotide.</p>	<p>\uparrow GH is normal in stress, exercise, and hypoglycemia.</p>
Hyperparathyroidism		
Primary	<p>Usually an adenoma. Hypercalcemia, hypercalciuria (renal stones), hypophosphatemia, \uparrow PTH, \uparrow cAMP in urine. Often asymptomatic, or may present with weakness and constipation (“groans”).</p>	<p>Osteitis fibrosa cystica (von Recklinghausen’s syndrome)—cystic bone spaces filled with brown fibrous tissue (bone pain).</p>
Secondary	<p>2° hyperplasia due to \downarrow serum Ca^{2+}, most often in chronic renal disease. Hypocalcemia, hyperphosphatemia, \uparrow PTH.</p>	<p>Renal osteodystrophy—bone lesions due to 2° hyperparathyroidism due in turn to renal disease. “Stones, bones, and groans.”</p>
Hypoparathyroidism	<p>Hypocalcemia, tetany. Due to accidental surgical excision (thyroid surgery) or DiGeorge syndrome. Chvostek’s sign—tap facial nerve \rightarrow contraction of facial muscles.</p> <p>Trousseau’s sign—occlusion of brachial artery with BP cuff \rightarrow carpal spasm.</p>	<p>Pseudohypoparathyroidism—autosomal-recessive kidney unresponsiveness to PTH. Hypocalcemia, shortened 4th/5th digits, short stature.</p>
Hypercalcemia	<p>Caused by Calcium ingestion (milk-alkali syndrome), Hyperparathyroid, Hyperthyroid, Iatrogenic (thiazides), Multiple myeloma, Paget’s disease, Addison’s disease, Neoplasms, Zollinger-Ellison syndrome, Excess vitamin D, Excess vitamin A, Sarcoidosis.</p>	<p>CHIMPANZEES.</p>

Diabetes mellitus

Acute manifestations Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2), unopposed secretion of GH and epinephrine (exacerbating hyperglycemia).



Chronic manifestations

Nonenzymatic glycosylation:

1. Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy (nodular sclerosis, progressive proteinuria, chronic renal failure, arteriosclerosis leading to hypertension)
2. Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease and gangrene, cerebrovascular disease

Osmotic damage:

1. Neuropathy (motor, sensory, and autonomic degeneration)
2. Cataracts (sorbitol accumulation)

Tests

Fasting serum glucose, glucose tolerance test, HbA_{1c} (measures long-term diabetic control).

Type 1 vs. type 2 diabetes mellitus

Variable	Type 1—juvenile onset (IDDM)	Type 2—adult onset (NIDDM)
1° defect	Viral or immune destruction of β cells (see Color Image 67)	↑ resistance to insulin
Insulin necessary in treatment	Always	Sometimes
Age (exceptions commonly occur)	< 30	> 40
Association with obesity	No	Yes
Genetic predisposition	Weak, polygenic	Strong, polygenic
Association with HLA system	Yes (HLA-DR3 and 4)	No
Glucose intolerance	Severe	Mild to moderate
Ketoacidosis	Common	Rare
β -cell numbers in the islets	↓	Variable
Serum insulin level	↓	Variable
Classic symptoms of polyuria, polydipsia, thirst, weight loss	Common	Sometimes

Diabetic ketoacidosis	One of the most important complications of type 1 diabetes. Usually due to an \uparrow in insulin requirements from an \uparrow in stress (e.g., infection). Excess fat breakdown and \uparrow ketogenesis from the \uparrow in free fatty acids, which are then made into ketone bodies.	
Signs/symptoms	Kussmaul respirations (rapid/deep breathing), hyperthermia, nausea/vomiting, abdominal pain, psychosis/dementia, dehydration. Fruity breath odor (due to exhaled acetone).	
Labs	Hyperglycemia, \uparrow H^+ , \downarrow HCO_3^- (anion gap metabolic acidosis), \uparrow blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K^+ .	
Complications	Life-threatening mucormycosis, <i>Rhizopus</i> infection, cerebral edema, cardiac arrhythmias, heart failure.	
Treatment	Fluids, insulin, and potassium; glucose if necessary to prevent hypoglycemia.	
Diabetes insipidus	Characterized by intensive thirst and polyuria together with an inability to concentrate urine owing to lack of ADH (central DI—pituitary tumor, trauma, surgery, histiocytosis X) or to a lack of renal response to ADH (nephrogenic DI—hereditary or 2° to hypercalcemia, lithium, demeclocycline).	
Diagnosis	Water deprivation test—urine osmolality doesn't \uparrow .	
Findings	Urine specific gravity < 1.006; serum osmolality > 290 mOsm/L.	
Treatment	Adequate fluid intake. For central DI—intranasal desmopressin (ADH analog). For nephrogenic DI—hydrochlorothiazide, indomethacin, or amiloride.	
SIADH	<p>Syndrome of inappropriate antidiuretic hormone secretion:</p> <ol style="list-style-type: none"> 1. Excessive water retention 2. Hyponatremia 3. Urine osmolality > serum osmolality <p>Very low serum sodium levels can lead to seizures (correct slowly).</p> <p>Treat with demeclocycline or H_2O restriction.</p>	<p>Causes include:</p> <ol style="list-style-type: none"> 1. Ectopic ADH (small cell lung cancer) 2. CNS disorders/head trauma 3. Pulmonary disease 4. Drugs (e.g., cyclophosphamide)
Carcinoid syndrome	<p>Rare syndrome caused by carcinoid tumors (neuroendocrine cells), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent diarrhea, cutaneous flushing, asthmatic wheezing, and right-sided valvular disease. Most common tumor of appendix. \uparrow 5-HIAA in urine.</p>	<p>Rule of 1/3s:</p> <p>1/3 metastasize</p> <p>1/3 present with 2nd malignancy</p> <p>1/3 multiple</p> <p>Derived from neuroendocrine cells of GI tract.</p> <p>Treat with octreotide.</p>
Zollinger-Ellison syndrome	Gastrin-secreting tumor of pancreas or duodenum. Causes recurrent ulcers. May be associated with MEN type I.	

Diabetes drugs

Treatment strategy for type 1 DM—low-sugar diet, insulin replacement.

Treatment strategy for type 2 DM—dietary modification and exercise for weight loss; oral hypoglycemics.

Drug Classes	Action	Clinical Use	Toxicities
Insulin: Lispro (short-acting) Insulin (short-acting) NPH (intermediate) Lente (long-acting) Ultralente (long-acting)	Binds insulin receptor (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen and protein synthesis, K ⁺ uptake. Fat: aids TG storage.	Type 1 DM. Also life-threatening hyperkalemia and stress-induced hyperglycemia.	Hypoglycemia, hypersensitivity reaction (very rare).
Sulfonylureas: First generation: Tolbutamide Chlorpropamide Second generation: Glyburide Glimepiride Glipizide	Close K ⁺ channel in β-cell membrane, so cell depolarizes → triggering of insulin release via ↑ Ca ²⁺ influx.	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	First generation: disulfiram-like effects. Second generation: hypoglycemia.
Biguanides: Metformin	Exact mechanism is unknown. Possibly ↓ gluconeogenesis , ↑ glycolysis, ↓ serum glucose levels.	Used as oral hypoglycemic. Can be used in patients without islet function.	Most grave adverse effect is lactic acidosis.
Glitazones: Pioglitazone Rosiglitazone	↑ target cell response to insulin.	Used as monotherapy in type 2 DM or combined with above agents.	Weight gain. Hepatotoxicity (troglitazone—no longer used).
α-glucosidase inhibitors: Acarbose Miglitol	Inhibit intestinal brush border α-glucosidases. Delayed sugar hydrolysis and glucose absorption lead to ↓ postprandial hyperglycemia.	Used as monotherapy in type 2 DM in combination with above agents.	GI disturbances.

Orlistat

Mechanism	Alters fat metabolism by inhibiting pancreatic lipases.
Clinical use	Long-term obesity management (in conjunction with modified diet).
Toxicity	Steatorrhea, GI discomfort, reduced absorption of fat-soluble vitamins, headache.

Sibutramine

Mechanism	Sympathomimetic serotonin and norepinephrine reuptake inhibitor.
Clinical use	Short-term and long-term obesity management.
Toxicity	Hypertension and tachycardia.

Propylthiouracil, methimazole

Mechanism	Inhibit organification and coupling of thyroid hormone synthesis. Propylthiouracil also ↓ peripheral conversion of T_4 to T_3 .
Clinical use	Hyperthyroidism.
Toxicity	Skin rash, agranulocytosis (rare), aplastic anemia.

Other hypothalamic/pituitary drugs

Drug	Clinical use
GH (somatostatin)	GH deficiency, Turner's syndrome
Octreotide	Acromegaly, carcinoid, gastrinoma, glucagonoma
Oxytocin	Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage
Desmopressin (ADH)	Pituitary (central, not nephrogenic) DI

Levothyroxine, triiodothyronine

Mechanism	Thyroxine replacement.
Clinical use	Hypothyroidism, myxedema.
Toxicity	Tachycardia, heat intolerance, tremors.

Glucocorticoids

Mechanism	Hydrocortisone, prednisone, triamcinolone, dexamethasone, beclomethasone. ↓ the production of leukotrienes and prostaglandins by inhibiting phospholipase A_2 and expression of COX-2.
Clinical use	Addison's disease, inflammation, immune suppression, asthma.
Toxicity	Iatrogenic Cushing's syndrome—buffalo hump, moon facies, truncal obesity, muscle wasting, thin skin, easy bruisability, osteoporosis, adrenocortical atrophy, peptic ulcers.

This image shows a full page of blank, lined paper. It features approximately 30 horizontal blue or grey lines spaced evenly apart, typical of notebook paper. The lines extend across the entire width of the page, leaving small margins at the top and bottom. There are no vertical lines, text, or other markings on the page.

Gastrointestinal

"I have flabby thighs, but fortunately my stomach covers them."

—Joan Rivers

"You thing of no bowels!"

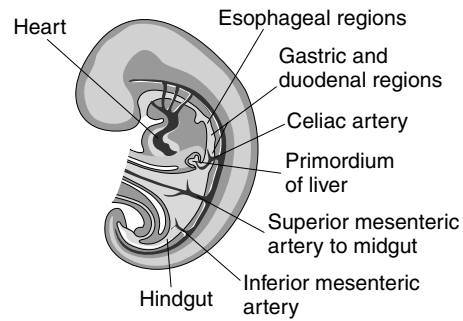
—Shakespearean insult

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

- | | | |
|--|-----------------------------------|--|
| ■ Baby vomits milk when fed and has a gastric air bubble. | What kind of fistula is present? | Blind esophagus with lower segment of esophagus attached to trachea. |
| ■ After a stressful life event, 30-year-old man has diarrhea and blood per rectum; intestinal biopsy shows transmural inflammation. | What is the diagnosis? | Crohn's. |
| ■ Young man presents with mental deterioration and tremors. He has brown pigmentation in a ring around the periphery of his cornea and altered LFTs. | What treatment should he receive? | Penicillamine for Wilson's disease. |
| ■ 20-year-old male presents with idiopathic hyperbilirubinemia. | What is the most common cause? | Gilbert's disease. |

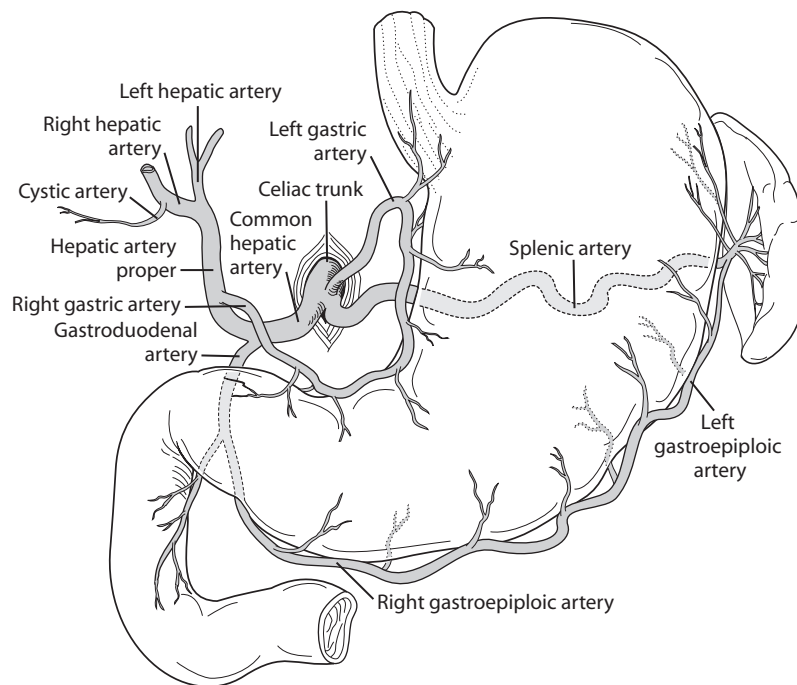
GI blood supply

Artery	Embryonic gut region	Structures supplied
Celiac	Foregut	Stomach to proximal duodenum; liver, gallbladder, pancreas
SMA	Midgut	Distal duodenum to proximal $\frac{2}{3}$ of transverse colon
IMA	Hindgut	Distal $\frac{1}{3}$ of transverse colon to upper portion of rectum

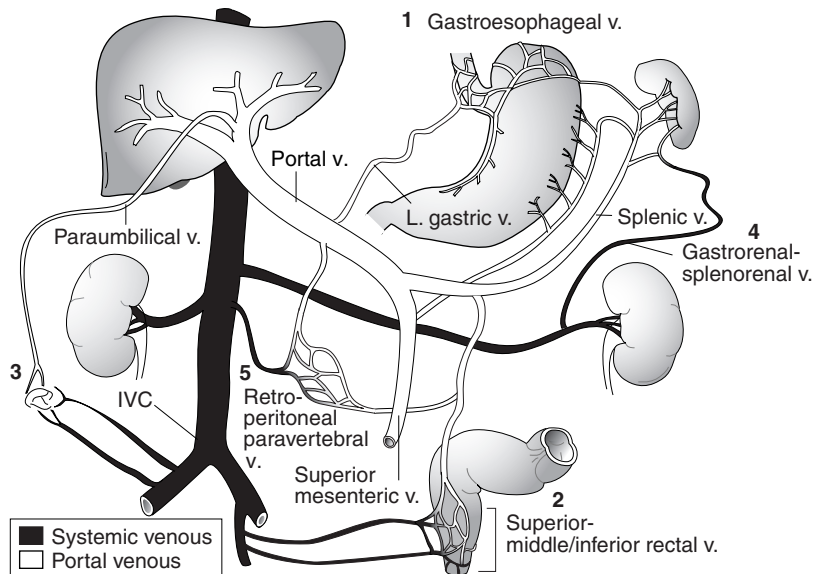


Celiac trunk

Stomach receives main blood supply from branches of the celiac trunk.



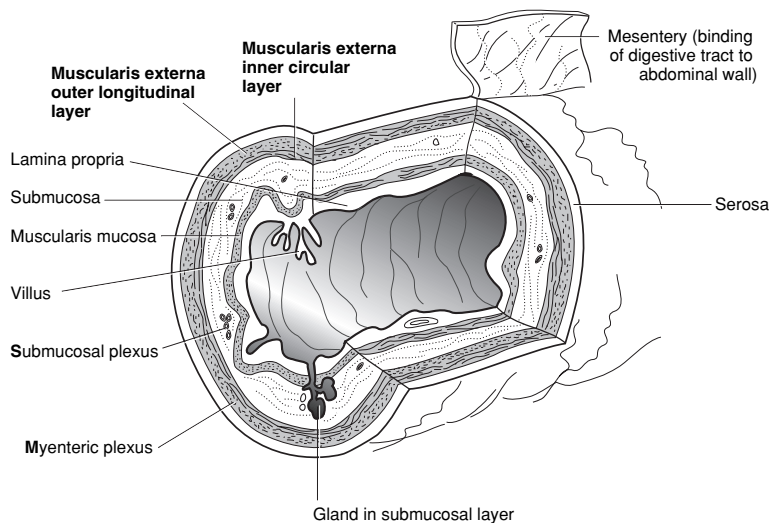
Portal-systemic anastomoses



1. Left gastric → azygous (esophageal varices)
2. Superior → inferior rectal (external hemorrhoids)
3. Paraumbilical → inferior epigastric (**caput medusae** at navel)
4. Retroperitoneal → renal
5. Retroperitoneal → paravertebral

Varices of **gut**, **butt**, and **caput** are commonly seen with portal hypertension.

Digestive tract anatomy

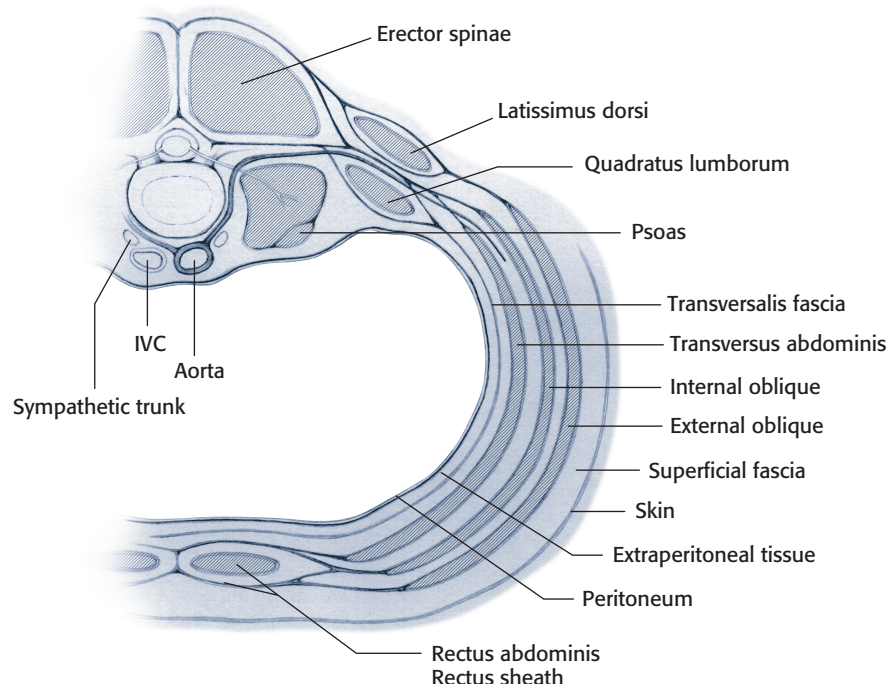


Layers of gut wall (inside to outside):

1. Mucosa—epithelium (absorption), lamina propria (support), muscularis mucosa (mucosal motility)
2. Submucosa—including Submucosal nerve plexus (Meissner's): controls Secretions, blood flow, and absorption
3. Muscularis externa—outer longitudinal layer, inner circular layer, Myenteric nerve plexus (Auerbach's): controls Motility
4. Serosa/adventitia

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:296.)

Abdominal layers



(Reproduced, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003:67.)

Enteric nerve plexi

Myenteric	Coordinates M otility along entire gut wall. Also known as Auerbach's plexus. Contains cell bodies of some parasympathetic terminal effector neurons. Located between inner and outer layers (longitudinal and circular) of smooth muscle in GI tract wall.
Submucosal	Regulates local S ecretions, blood flow, and absorption. Also known as Meissner's plexus. Contains cell bodies of some parasympathetic terminal effector neurons. Located between mucosa and inner layer of smooth muscle in GI tract wall.

Brunner's glands

Secrete alkaline mucus to neutralize acid contents entering the duodenum from the stomach. Located in duodenal submucosa (the only GI submucosal glands). Hypertrophy of Brunner's glands seen in peptic ulcer disease.

Peyer's patch

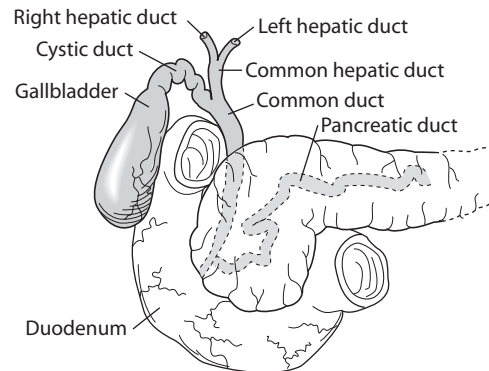
Unencapsulated lymphoid tissue found in lamina propria and submucosa of small intestine. Covered by single layer of cuboidal enterocytes (no goblet cells) with specialized M cells interspersed. M cells take up antigen. Stimulated B cells leave Peyer's patch and travel through lymph and blood to lamina propria of intestine, where they differentiate to IgA-secreting plasma cells. IgA receives protective secretory component and is then transported across epithelium to gut to deal with intraluminal antigen.

Think of **IgA**, the **I**ntra-gut **A**ntibody. And always say "secretory IgA."

Sinusoids of liver

Irregular “capillaries” with fenestrated endothelium (pores 100–200 nm in diameter). No basement membrane. Allows macromolecules of plasma full access to basal surface of hepatocytes through perisinusoidal space (space of Disse).

Biliary structures



Pectinate line

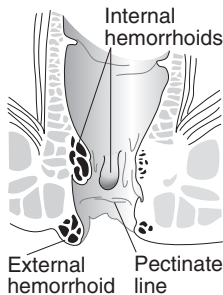
Formed where hindgut meets ectoderm.

Above pectinate line—internal hemorrhoids (not painful), adenocarcinoma. Visceral innervation. Arterial supply is from the superior rectal artery (branch of IMA). Venous drainage is to superior rectal vein → inferior mesenteric vein → portal system.

Internal hemorrhoids receive visceral innervation.

Below pectinate line—external hemorrhoids (painful), squamous cell carcinoma. Somatic innervation. Arterial supply is from the inferior rectal artery (branch of internal pudendal artery). Venous drainage is to inferior rectal vein → internal pudendal vein → internal iliac vein → IVC.

External hemorrhoids receive somatic innervation and are therefore painful.



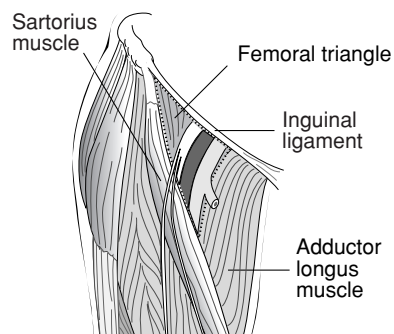
Femoral triangle

Femoral triangle contains femoral vein, femoral artery, and femoral nerve. Femoral sheath—fascial tube extending 3–4 cm below inguinal ligament; contains femoral artery, femoral vein, and femoral canal (containing deep inguinal lymph nodes). Femoral nerve lies outside femoral sheath.

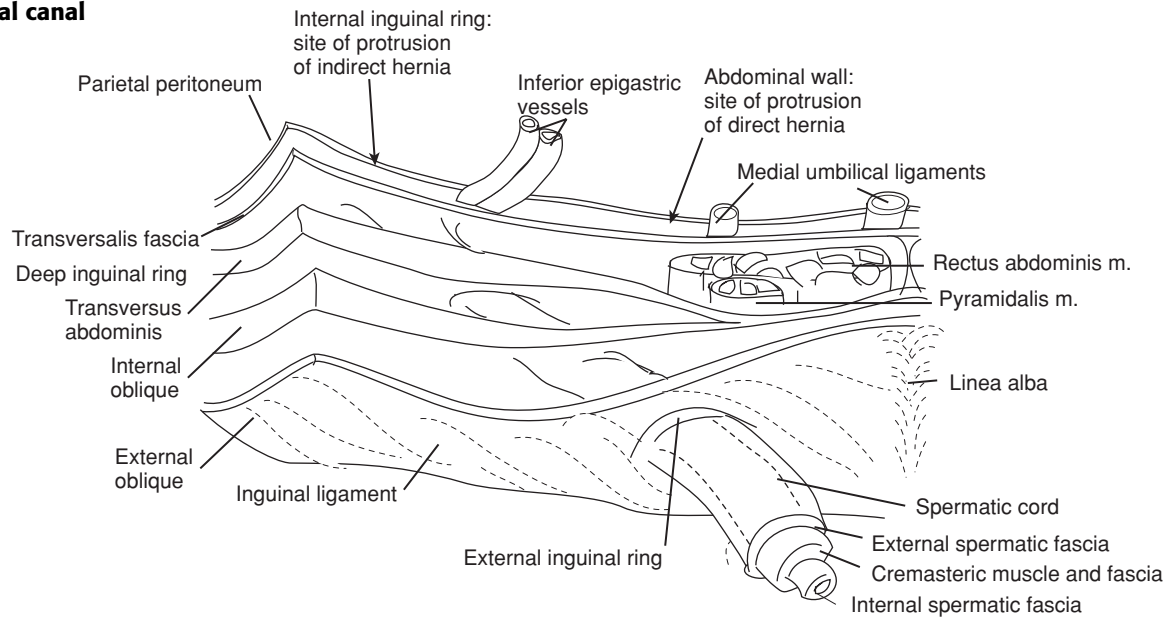
Lateral to medial: **N**–(**AVEL**) = **Nerve**–(**Artery**–**Vein**–**Empty space**–**Lymphatics**).

Femoral hernia is entrance of abdominal contents through the femoral canal.

Femoral hernia protrudes below and lateral to the pubic tubercle.



Inguinal canal



(Adapted, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003:69.)

Salivary secretion

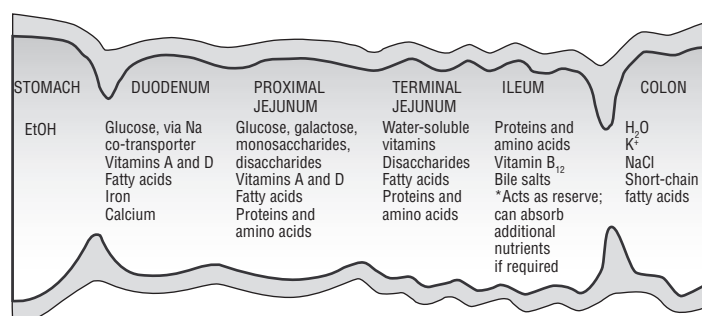
Source	Parotid, submandibular, submaxillary, and sublingual glands.	Salivary secretion is stimulated by both sympathetic (T1–T3 superior cervical ganglion) and parasympathetic (facial, glossopharyngeal nerve) activity. Low flow rate → hypotonic. High flow rate → closer to isotonic.
Function	<ol style="list-style-type: none"> 1. α-amylase (ptyalin) begins starch digestion; inactivated by low pH on reaching stomach 2. Bicarbonate neutralizes oral bacterial acids, maintains dental health 3. Mucins (glycoproteins) lubricate food 	

GI secretory products

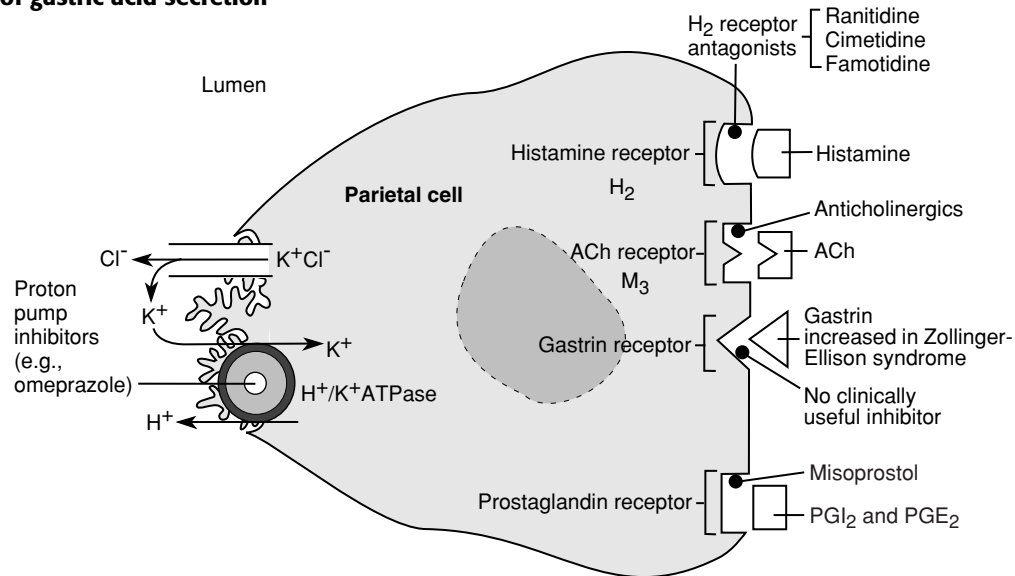
Product	Source	Action	Regulation	Notes
Intrinsic factor	Parietal cells, stomach	Vitamin B ₁₂ binding protein (required for B ₁₂ uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia
Gastric acid	Parietal cells, stomach	↓ stomach pH	↑ by histamine, ACh, gastrin; ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells, stomach	Protein digestion; optimal function at pH 1.0–3.0	↑ by vagal stimulation, local acid	Inactive pepsinogen → pepsin by H ⁺
HCO ₃ ⁻	Mucosal cells, stomach and duodenum	Neutralizes acid; prevents autodigestion	↑ by secretin	

GI hormones

Hormone	Source	Action	Regulation	Notes
Gastrin	G cells, antrum of stomach	↑ gastric H ⁺ secretion, ↑ growth of gastric mucosa, ↑ gastric motility	↑ by stomach distention, amino acids, peptides, vagal stimulation; ↓ by H ⁺ secretion and stomach acid pH < 1.5	↑↑ in Zollinger-Ellison syndrome; phenylalanine and tryptophan are potent stimulators
Cholecystokinin	I cells, duodenum, jejunum	↑ pancreatic secretion, ↑ gallbladder contraction; ↓ gastric emptying, ↑ growth of exocrine pancreas and gallbladder	↓ by secretin and stomach pH < 1.5; ↑ by fatty acids, amino acids	In cholelithiasis, pain worsens after fatty food ingestion due to ↑ CCK
Secretin	S cells, duodenum	↑ pancreatic HCO ₃ ⁻ secretion, ↓ gastric acid secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO ₃ ⁻ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function
Somatostatin	D cells, pancreatic islets; GI mucosa	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid; ↓ by vagal stimulation	Inhibitory hormone; antigrowth hormone effects (digestion and absorption of substances needed for growth)
Gastric inhibitory peptide (GIP)	K cells, duodenum and jejunum	Exocrine: ↓ gastric H ⁺ secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose (only GI hormone stimulated by all 3 nutrient classes)	↑ GIP is why an oral glucose load is used more rapidly than the equivalent given by IV

Nutrient absorption

Regulation of gastric acid secretion



Pancreatic enzymes

α -amylase—starch digestion, secreted in active form.

Lipase, phospholipase A, colipase—fat digestion.

Proteases (trypsin, chymotrypsin, elastase, carboxypeptidases)—protein digestion, secreted as proenzymes.

Trypsinogen is converted to active enzyme trypsin by enterokinase, a duodenal brush-border enzyme. Trypsin then activates the other proenzymes and can also activate trypsinogen (positive feedback loop).

Pancreatic insufficiency is seen in cystic fibrosis and other conditions. Patients present with malabsorption, steatorrhea (greasy, malodorous stool). Limit fat intake, monitor for signs of fat-soluble vitamin (A, D, E, K) deficiency.

Carbohydrate digestion

Only monosaccharides (glucose, galactose, fructose) are absorbed.

Salivary amylase

Starts digestion, hydrolyzes α -1,4 linkages to yield disaccharides (maltose, maltotriose, and α -limit dextrins).

Pancreatic amylase

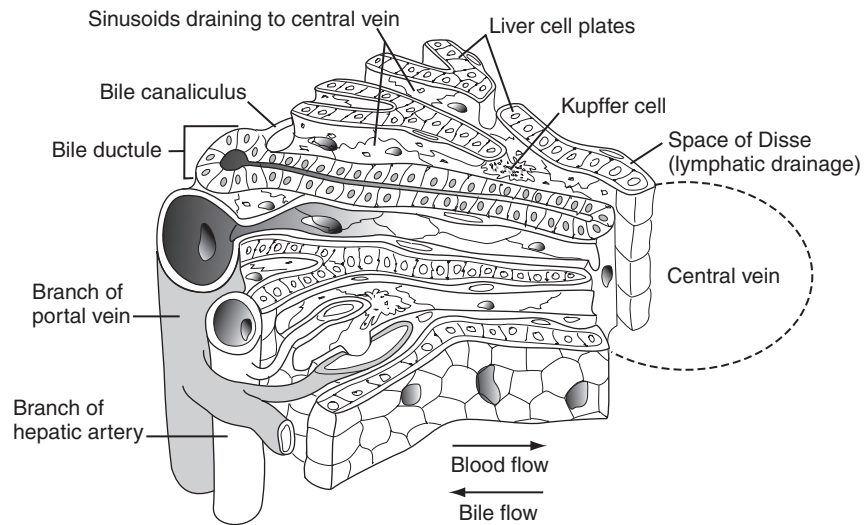
Highest concentration in duodenal lumen, hydrolyzes starch to oligosaccharides and disaccharides.

Oligosaccharide hydrolases

At brush border of intestine, the rate-limiting step in carbohydrate digestion, produce monosaccharides from oligo- and disaccharides.

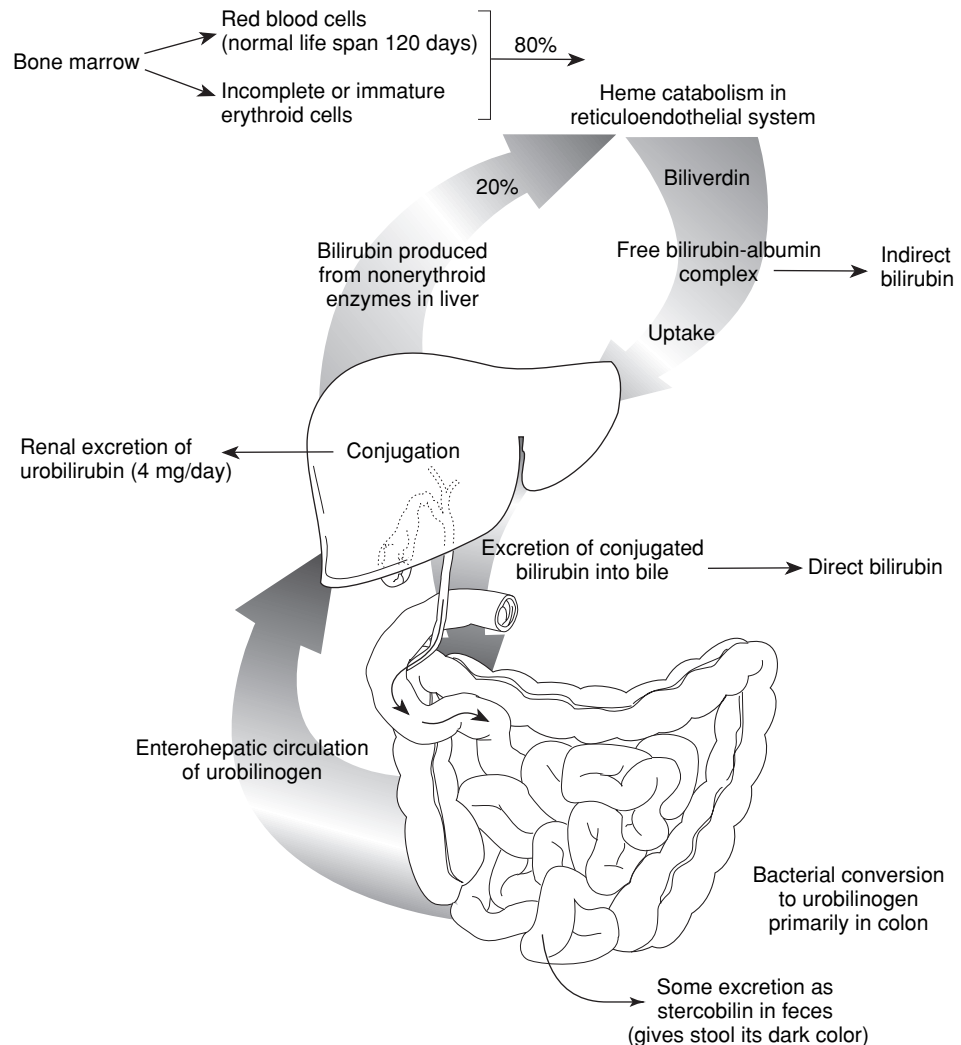
Liver anatomy

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.



Bilirubin

Product of heme metabolism; actively taken up by hepatocytes. Direct bilirubin—conjugated with glucuronic acid; water soluble. Indirect bilirubin—unconjugated; water insoluble. Jaundice (yellow skin, sclerae) results from elevated bilirubin levels.

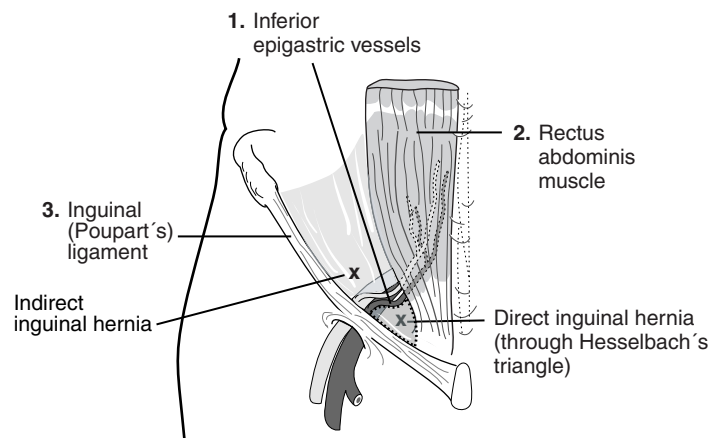


Bile

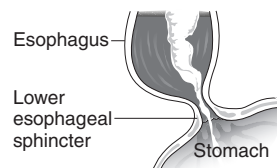
Composed of bile salts (bile acids conjugated to glycine or taurine to make them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. The only significant mechanism for cholesterol excretion.

Abdominal hernias

Diaphragmatic hernia	Hernias are protrusions of peritoneum through an opening, usually sites of weakness. Abdominal structures enter the thorax; may occur in infants as a result of defective development of pleuroperitoneal membrane. Most commonly a hiatal hernia, in which stomach herniates upward through the esophageal hiatus of the diaphragm.	MDs don't LLe: Medial to inferior epigastric artery = Direct hernia. Lateral to inferior epigastric artery = Indirect hernia.
Indirect inguinal hernia	INDirect hernia goes through the INternal (deep) inguinal ring and external (superficial) inguinal ring and INto the scrotum. Indirect hernia enters internal inguinal ring lateral to inferior epigastric artery. INDirect hernias occur in INFants owing to failure of processus vaginalis to close. Much more common in males.	
Direct inguinal hernia	Protrudes through the inguinal (Hesselbach's) triangle. Direct hernia bulges directly through abdominal wall medial to inferior epigastric artery. Goes through the external (superficial) inguinal ring only. Usually in older men.	Hesselbach's triangle: Inferior epigastric artery Lateral border of rectus abdominis Inguinal ligament



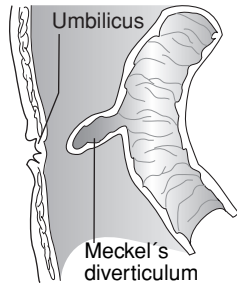
Achalasia



Failure of relaxation of lower esophageal sphincter due to loss of myenteric (Auerbach's) plexus. Causes progressive dysphagia. Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with an ↑ risk of esophageal carcinoma.

Achalasia = absence of relaxation.
2° achalasia may arise from Chagas' disease.
"Bird beak" on barium swallow.

Meckel's diverticulum



Persistence of the vitelline duct or yolk stalk. May contain ectopic acid-secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of the GI tract. Can cause bleeding, intussusception, volvulus, or obstruction near the terminal ileum. Contrast with omphalomesenteric cyst = cystic dilatation of vitelline duct.

The five 2's:
 2 inches long.
 2 feet from the ileocecal valve.
 2% of population.
 Commonly presents in first 2 years of life.
 May have 2 types of epithelia.

Enzyme markers of GI pathology

Serum enzyme
 Aminotransferases (AST and ALT)

GGT (γ -glutamyl transpeptidase)
 Alkaline phosphatase

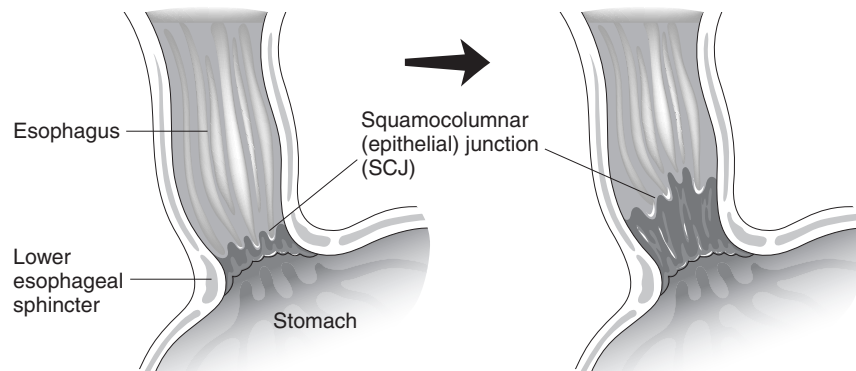
Amylase
 Lipase
 Ceruloplasmin (\downarrow)

Major diagnostic use
 Viral hepatitis (ALT > AST)
 Alcoholic hepatitis (AST > ALT)
 Myocardial infarction (AST only)
 Various liver diseases
 Obstructive liver disease (hepatocellular carcinoma), bone disease
 Acute pancreatitis, mumps
 Acute pancreatitis
 Wilson's disease (see Color Image 51)

Barrett's esophagus

Glandular (columnar epithelial) metaplasia—replacement of nonkeratinized squamous epithelium with gastric (columnar) epithelium in the distal esophagus. Due to chronic acid reflux.

BARrett's = Becomes Adenocarcinoma, Results from Reflux.



Esophageal cancer	<p>Risk factors for esophageal cancer are:</p> <ul style="list-style-type: none"> Alcohol Barrett's esophagus Cigarettes Diverticuli (e.g., Zenker's diverticulum) Esophageal web (e.g., Plummer-Vinson)/ Esophagitis (due to reflux, irritants, infection) Familial 	<p>ABCDEF.</p> <p>Usually squamous cell carcinoma (Barrett's leads to adenocarcinoma).</p>
Congenital pyloric stenosis	<p>Hypertrophy of the pylorus causes obstruction. Palpable "olive" mass in epigastric region and nonbilious projectile vomiting at \approx 2 weeks of age. Treatment is surgical incision. Occurs in 1/600 live births, often in 1st-born males.</p>	
Malabsorption syndromes	<p>Can cause diarrhea, steatorrhea, weight loss, weakness.</p>	
<ul style="list-style-type: none"> Celiac sprue Tropical sprue Whipple's disease 	<p>Autoantibodies to gluten (gliadin) in wheat and other grains. Proximal small bowel only. Probably infectious; responds to antibiotics. Can affect entire small bowel.</p> <p>Infection with <i>Tropheryma whippelii</i>; PAS-positive macrophages in intestinal lamina propria, mesenteric nodes.</p>	
<ul style="list-style-type: none"> Disaccharidase deficiency Pancreatic insufficiency 	<p>Most common is lactase deficiency \rightarrow milk intolerance.</p> <p>Due to CF, chronic pancreatitis. Causes malabsorption of protein, fat, vitamins A, D, E, K.</p>	
Gastritis		
Acute gastritis (erosive)	<p>Disruption of mucosal barrier \rightarrow inflammation. Can be caused by stress, NSAIDs, alcohol, uricemia, burns (Curling's ulcer), and brain injury (Cushing's ulcer).</p>	
Chronic gastritis (nonerosive)		
Type A (fundal)	<p>Autoimmune disorder characterized by</p> <ul style="list-style-type: none"> Autoantibodies to parietal cells, pernicious Anemia, and Achlorhydria. 	Type A = 4 A's.
Type B (antral)	<p>Caused by <i>H. pylori</i> infection.</p>	<p>Type B = a Bug, <i>H. pylori</i>.</p> <p>Both carry \uparrow risk of gastric carcinoma.</p>

Peptic ulcer disease

Gastric ulcer	Pain Greater with meals—weight loss. <i>H. pylori</i> infection in 70%; chronic NSAID use also implicated. Due to ↓ mucosal protection against gastric acid.
Duodenal ulcer	Pain Decreases with meals—weight gain. Almost 100% have <i>H. pylori</i> infection. Due to ↑ gastric acid secretion or ↓ mucosal protection. Hypertrophy of Brunner's glands. Tend to have clean, “punched-out” margins unlike the raised/irregular margins of carcinoma. Potential complications include bleeding, penetration, perforation, and obstruction (not intrinsically precancerous). <i>H. pylori</i> infection can be treated with “triple therapy” (metronidazole, bismuth salicylate, and either amoxicillin or tetracycline) with or without a proton pump inhibitor. Incidence of peptic ulcer disease is twice as great in smokers (see Image 111).

Stomach cancer	Almost always adenocarcinoma. Early aggressive local spread and node/liver mets. Associated with dietary nitrosamines, achlorhydria, chronic gastritis. Termed linitis plastica when diffusely infiltrative (thickened, rigid appearance).	Virchow's node—involvement of supraclavicular node by mets from stomach. Krukenberg's tumor—bilateral mets to ovaries. Abundant mucus, “signet-ring” cells.
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Inflammatory bowel disease

	Crohn's disease	Ulcerative colitis
Possible etiology	Infectious.	Autoimmune.
Location	May involve any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing.	<i>Colitis</i> = colon inflammation. Continuous lesions, always with rectal involvement.
Gross morphology	Transmural inflammation. Cobblestone mucosa, creeping fat , bowel wall thickening (“string sign” on barium swallow x-ray), linear ulcers, fissures, fistulas.	Mucosal and submucosal inflammation only. Friable mucosal pseudopolyps with freely hanging mesentery.
Microscopic morphology	Noncaseating granulomas and lymphoid aggregates.	Crypt abscesses and ulcers, bleeding, no granulomas.
Complications	Strictures, fistulas, perianal disease, malabsorption, nutritional depletion.	Severe stenosis, toxic megacolon, colorectal carcinoma .
Extraintestinal manifestations	Migratory polyarthritis, erythema nodosum, ankylosing spondylitis, uveitis, immunologic disorders.	Pyoderma gangrenosum, 1° sclerosing cholangitis.

For **Crohn's**, think of a **fat granny** and an old **crone skipping** down a **cobblestone** road away from the **wreck** (rectal sparing) (see Images 114, 115).

Appendicitis

All age groups; most common indication for emergent abdominal surgery in children. Initial diffuse periumbilical pain → localized pain at McBurney's point. Nausea, fever; may perforate → peritonitis.
Differential: diverticulitis (elderly), ectopic pregnancy (use β-hCG to rule out).

Diverticular disease**Diverticulum**

Blind pouch leading off the alimentary tract, lined by mucosa, muscularis, and serosa, that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed “false” in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.

“True” diverticulum—all 3 gut wall layers outpouch.

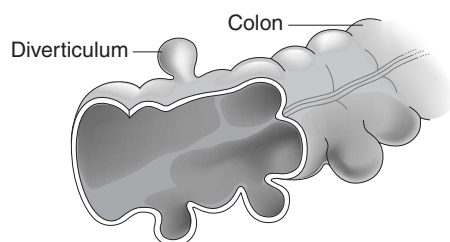
“False” diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.

Diverticulosis

The prevalence of diverticulosis (many diverticula) in patients > 60 years of age approaches 50%. Caused by ↑ intraluminal pressure and focal weakness in the colonic wall. Most frequently involves the sigmoid colon. Associated with low-fiber diets. Most often asymptomatic or associated with vague discomfort and/or rectal bleeding.

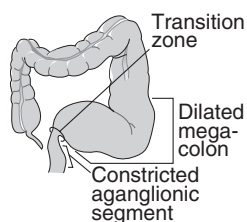
Diverticulitis

Inflammation of diverticula classically causing LLQ pain. May → perforation, peritonitis, abscess formation, or bowel stenosis (see Color Image 31).

**Intussusception and volvulus**

Intussusception—“telescoping” of 1 bowel segment into distal segment; can compromise blood supply (see Color Image 34). Often due to intraluminal mass.

Volvulus—twisting of portion of bowel around its mesentery; can lead to obstruction and infection. May occur at sigmoid colon, where there is redundant mesentery.

Hirschsprung's disease

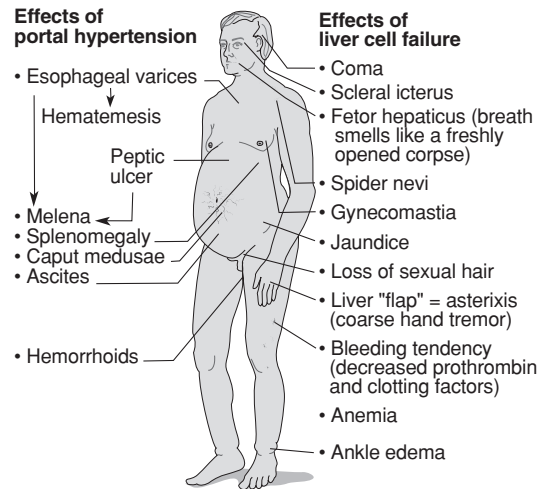
Congenital megacolon characterized by lack of enteric nervous plexus in segment (Auerbach's and Meissner's plexuses) on intestinal biopsy. Due to failure of neural crest cell migration. Presents as chronic constipation early in life. Dilated portion of the colon proximal to the aganglionic segment, resulting in a “transition zone.”

Think of a giant spring that has **sprung** in the colon.
Risk ↑ with Down syndrome.

Colorectal cancer

3rd most common cancer. Risk factors—colorectal villous adenomas, chronic inflammatory bowel disease (especially ulcerative colitis), high-fat and low-fiber diets, ↑ age, familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC), DCC gene deletion, personal and family history of colon cancer. Peutz-Jeghers, a benign polyposis syndrome, is not a risk factor. Screen patients > 50 years old with stool occult blood test, colonoscopy. Visualized on barium swallow x-ray as “apple core” lesion. CEA—nonspecific tumor marker.

Cirrhosis and portal hypertension



(Adapted, with permission, from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:654.)

Cirrho (Greek) = tawny yellow. Diffuse fibrosis of liver, destroys normal architecture.

Nodular regeneration.

Micronodular—nodules < 3 mm, uniform size. Due to metabolic insult (e.g., alcohol, hemochromatosis, Wilson's disease).

Macronodular—nodules > 3 mm, varied size. Usually due to significant liver injury leading to hepatic necrosis (e.g., postinfectious or drug-induced hepatitis). ↑ risk of hepatocellular carcinoma.

Portacaval shunt between splenic vein and left renal vein may relieve portal hypertension (see Color Image 29).

Alcoholic hepatitis

Swollen and necrotic hepatocytes, neutrophil infiltration, Mallory bodies (intracytoplasmic eosinophilic inclusions), fatty change, and sclerosis around central vein. SGOT (AST) to SGPT (ALT) ratio is usually > 1.5.

A Scotch and Tonic:

AST elevated (> ALT) with alcoholic hepatitis.

ALT > AST in viral hepatitis.

Budd-Chiari syndrome

Occlusion of IVC or hepatic veins with centrilobular congestion and necrosis, leading to congestive liver disease (hepatomegaly, ascites, abdominal pain, and eventual liver failure). Associated with polycythemia vera, pregnancy, hepatocellular carcinoma.

Wilson's disease

Inadequate hepatic copper excretion and failure of copper to enter circulation as ceruloplasmin. Leads to copper accumulation, especially in liver, brain, cornea, kidneys, joints. Also known as hepatolenticular degeneration.

Wilson's disease is characterized by:

Asterixis

Basal ganglia degeneration (parkinsonian symptoms)

Ceruloplasmin ↓, Cirrhosis, Corneal deposits (Kayser-Fleischer rings), Copper accumulation, Carcinoma (hepatocellular), Choreiform movements

Dementia

Treat with penicillamine.

Autosomal-recessive inheritance.

ABCD.

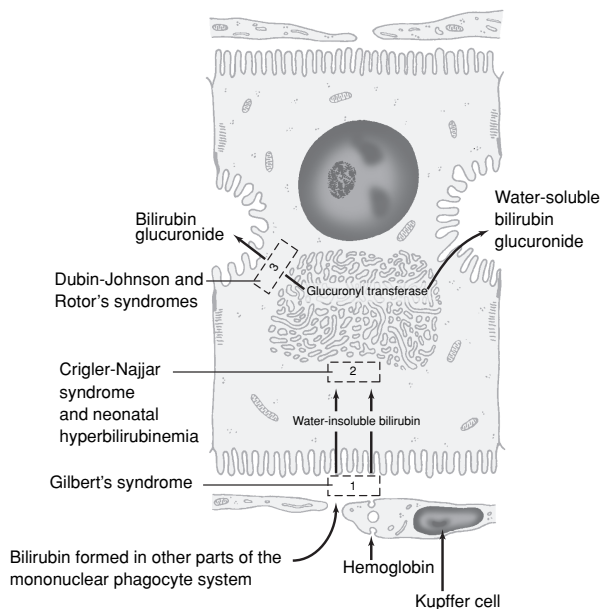
Hemochromatosis	Hemosiderosis is the deposition of hemosiderin (iron); hemochromatosis is the disease caused by this iron deposition. Classic triad of micronodular cirrhosis, pancreatic fibrosis, and skin pigmentation → “bronze” diabetes. Results in CHF and ↑ risk of hepatocellular carcinoma. Disease may be 1° (autosomal recessive) or 2° to chronic transfusion therapy. ↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation (see Color Image 26).	Total body iron may reach 50 g, enough to set off metal detectors at airports. Treat with repeated phlebotomy, deferoxamine.
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Jaundice Normally, liver cells convert unconjugated (indirect) bilirubin into conjugated (direct) bilirubin. Direct bilirubin is water soluble and can be excreted into urine and by the liver into bile to be converted by gut bacteria to urobilinogen (some of which is reabsorbed). Some urobilinogen is also formed directly from heme metabolism.

Jaundice type	Hyperbilirubinemia	Urine bilirubin	Urine urobilinogen
Hepatocellular	Conjugated/unconjugated	↑	Normal/↓
Obstructive	Conjugated	↑	↓
Hemolytic	Unconjugated	Absent (acholuria)	↑

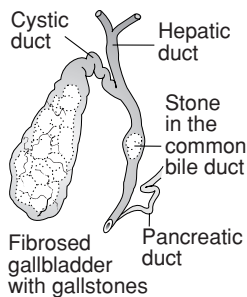
Hereditary hyperbilirubinemias

Gilbert's syndrome	Mildly ↓ UDP-glucuronyl transferase. Asymptomatic, but unconjugated bilirubin is elevated without overt hemolysis. Associated with stress.	Gilbert's has no clinical consequences.
Crigler-Najjar syndrome, type I	Absent UDP-glucuronyl transferase. Presents early in life; patients die within a few years. Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy.	Crigler-Najjar type I is a severe disease. Type II is less severe and responds to phenobarbital.
Dubin-Johnson syndrome	Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.	Rotor's syndrome is similar but even milder and does not cause black liver.



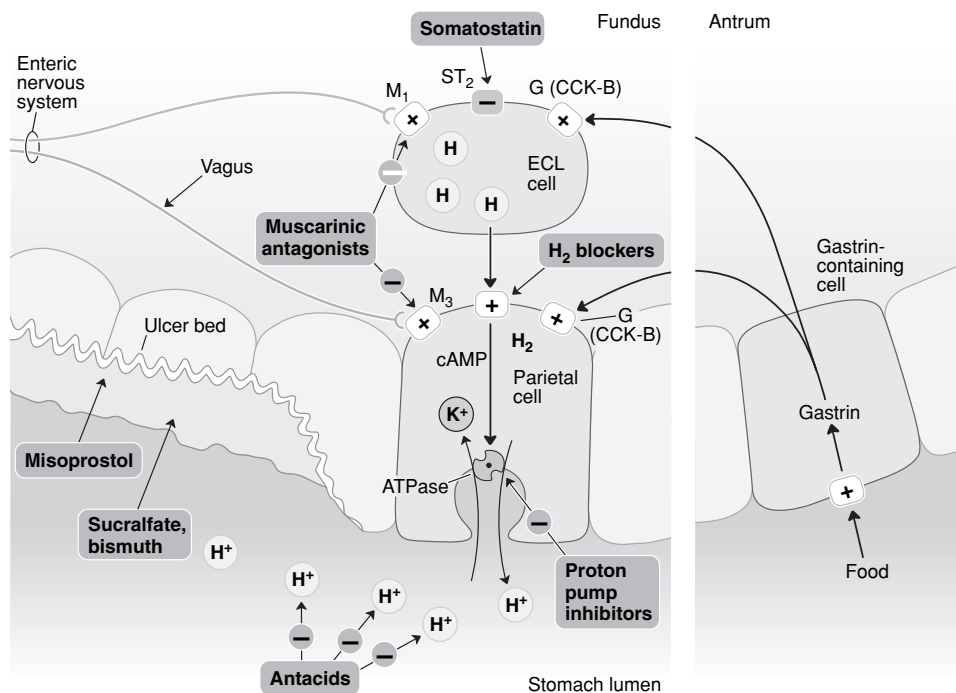
(Adapted, with permission, from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology*, 9th ed. Stamford, CT: Appleton & Lange, 1999.)

Primary sclerosing cholangitis	Both intra- and extrahepatic. Inflammation and fibrosis of bile ducts → alternating strictures and dilation with “beading” on ERCP. Associated with ulcerative colitis. Can lead to 2° biliary cirrhosis.	Charcot’s triad of cholangitis: 1. Jaundice 2. Fever 3. RUQ pain
Biliary cirrhosis		
Primary	Intrahepatic, autoimmune disorder; severe obstructive jaundice, steatorrhea, pruritus, hypercholesterolemia (xanthoma). ↑ alkaline phosphatase, ↑ serum mitochondrial antibodies.	
Secondary	Due to extrahepatic biliary obstruction. ↑ in pressure in intrahepatic ducts → injury/fibrosis. Often complicated by ascending cholangitis (bacterial infection), bile stasis, and “bile lakes.” ↑ alkaline phosphatase, ↑ conjugated bilirubin.	
Hepatocellular carcinoma	Also called hepatoma. Most common 1° malignant tumor of the liver in adults. ↑ incidence of hepatocellular carcinoma is associated with hepatitis B and C, Wilson’s disease, hemochromatosis, α_1 -antitrypsin deficiency, alcoholic cirrhosis, and carcinogens (e.g., aflatoxin B1). Can present with tender hepatomegaly, ascites, polycythemia, and hypoglycemia.	Hepatocellular carcinoma, like renal cell carcinoma, is commonly spread by hematogenous dissemination. Elevated α -fetoprotein. May lead to Budd-Chiari syndrome.
Reye’s syndrome	Rare, often fatal childhood hepatoencephalopathy. Findings: fatty liver (microvesicular fatty change), hypoglycemia, coma. Associated with viral infection (especially VZV and influenza B) and salicylates; thus, aspirin is no longer recommended for children (use acetaminophen, with caution).	
Gallstones	Form when solubilizing bile acids and lecithin are overwhelmed by ↑ cholesterol and/or bilirubin. Three types of stones: 1. Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—associated with obesity, Crohn’s disease, cystic fibrosis, advanced age, clofibrate, estrogens, multiparity, rapid weight loss, and Native American origin. 2. Mixed stones (radiolucent)—have both cholesterol and pigment components. Most common type. 3. Pigment stones (radiopaque)—seen in patients with chronic RBC hemolysis, alcoholic cirrhosis, advanced age, and biliary infection. Diagnose with ultrasound. Treat with cholecystectomy.	Risk factors (4 F’s): 1. Female 2. Fat 3. Fertile 4. Forty



Acute pancreatitis	<p>Caused by activation of pancreatic enzymes → autodigestion.</p> <p>Causes: Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hyperlipidemia, Drugs (e.g., sulfa drugs).</p> <p>Clinical presentation: epigastric abdominal pain radiating to back; anorexia, nausea.</p> <p>Labs: elevated amylase, lipase (higher specificity).</p> <p>Can lead to DIC, ARDS, diffuse fat necrosis, hypocalcemia, pseudocyst formation, hemorrhage, and infection.</p> <p>Chronic calcifying pancreatitis is strongly associated with alcoholism (see Image 135). Chronic obstructive pancreatitis is strongly associated with gallstones.</p>	<p>GET SMASHeD.</p> <p>ddI can cause a fatal pancreatitis!</p>
Pancreatic adenocarcinoma	<p>Prognosis averages 6 months or less; very aggressive; usually already metastasized at presentation; tumors more common in pancreatic head (obstructive jaundice).</p> <p>Often presents with:</p> <ol style="list-style-type: none"> 1. Abdominal pain radiating to back 2. Weight loss (due to malabsorption and anorexia) 3. Migratory thrombophlebitis (Trousseau's syndrome) 4. Obstructive jaundice with palpable gallbladder (Courvoisier's sign) (see Image 134) 	

GI therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:159.)

H₂ blockers

Mechanism
Clinical use
Toxicity

Cimetidine, ranitidine, famotidine, nizatidine.
Reversible block of histamine H₂ receptors → ↓ H⁺ secretion by parietal cells.
Peptic ulcer, gastritis, mild esophageal reflux.
Cimetidine is a potent inhibitor of P-450; it also has an antiandrogenic effect and ↓ renal excretion of creatinine. Other H₂ blockers are relatively free of these effects.

Proton pump inhibitors

Mechanism
Clinical use

Omeprazole, lansoprazole.
Irreversibly inhibit H⁺/K⁺ ATPase in stomach parietal cells.
Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.

Bismuth, sucralfate

Mechanism
Clinical use

Bind to ulcer base, providing physical protection, and allow HCO₃⁻ secretion to reestablish pH gradient in the mucus layer.
↑ ulcer healing, traveler's diarrhea.

Triple therapy of *H. pylori* ulcers—metronidazole, bismuth, amoxicillin (or tetracycline).

Misoprostol

Mechanism
Clinical use
Toxicity

A PGE₁ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.
Prevention of NSAID-induced peptic ulcers; maintenance of a patent ductus arteriosus. Also used to induce labor.
Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

Muscarinic antagonists	
Mechanism	Pirenzepine, propantheline. Block M1 receptors on ECL cells (↓ histamine secretion) and M3 receptors on parietal cells (↓ H ⁺ secretion).
Clinical use	Peptic ulcer.
Toxicity	Bradycardia, dry mouth, difficulty focusing eyes.
Infliximab	
Mechanism	A monoclonal antibody to TNF- α , proinflammatory cytokine.
Clinical use	Crohn's disease, rheumatoid arthritis.
Toxicity	Respiratory infection, fever, hypotension.
Sulfasalazine	
Mechanism	A combination of sulfapyridine (antibacterial) and mesalamine (anti-inflammatory). Activated by colonic bacteria.
Clinical use	Ulcerative colitis, Crohn's disease.
Toxicity	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.
Ondansetron	
Mechanism	5-HT ₃ antagonist. Powerful central-acting antiemetic.
Clinical use	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.
Toxicity	Headache, constipation.
Antacid overuse	
Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.	
Overuse can also cause the following problems:	
<ol style="list-style-type: none"> 1. Aluminum hydroxide—constipation and hypophosphatemia 2. Magnesium hydroxide—diarrhea 3. Calcium carbonate—hypercalcemia, rebound acid ↑ 	
All can cause hypokalemia.	
<p>You will not vomit with ONDANSetron, so you can go ON DANCing.</p> <p>Aluminum amount of feces. Mg = Must go to the bathroom.</p>	

NOTES

This image shows a full page of blank, lined paper. It features approximately 28 horizontal blue or grey lines spaced evenly apart, typical of standard notebook paper. The lines extend across the entire width of the page, leaving small margins at the top and bottom. There are no vertical lines, text, or other markings present.

Hematology and Oncology

“The best blood will at some time get into a fool or mosquito.”

—Austin O’Malley

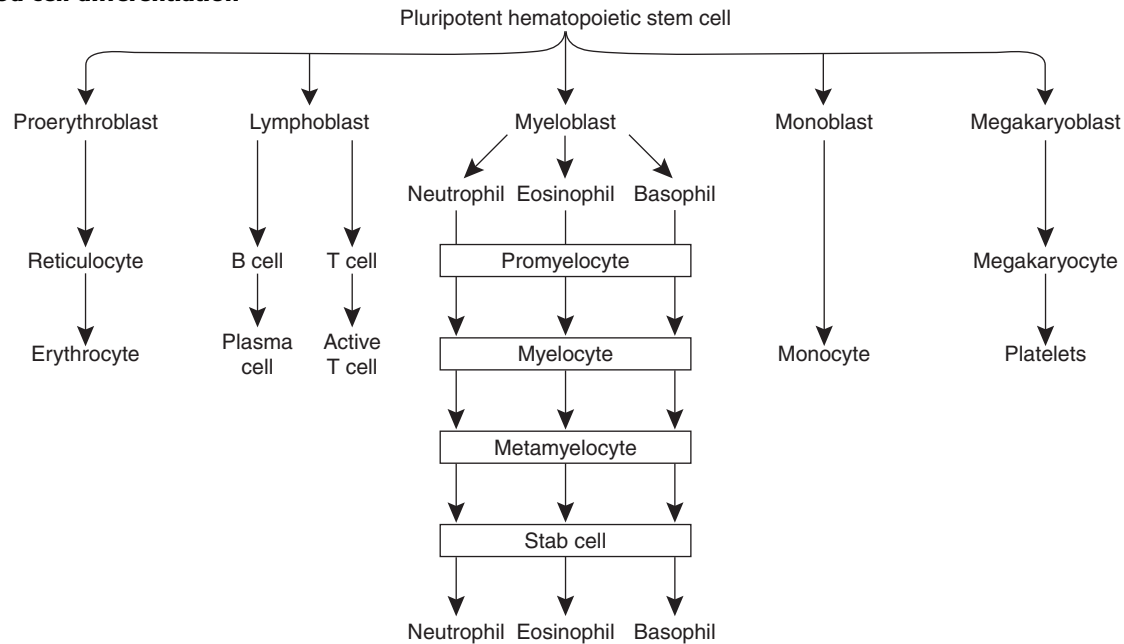
“A day without blood is like a day without sunshine.”

—Joker in *Full Metal Jacket*

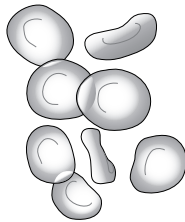
- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

- | | | |
|---|---|--|
| ■ Child has been anemic since birth. | Splenectomy would result in ↑ hematocrit in what disease? | Spherocytosis. |
| ■ Patient presents with fatigue, and blood tests show a macrocytic, megaloblastic anemia. | What is the danger of giving folate alone? | Masks signs of neural damage with vitamin B ₁₂ deficiency. |
| ■ Patient presents with anemia, hypercalcemia, and bone pain on palpation; bone marrow biopsy shows a slide packed with cells that have a large, round, off-center nucleus. | What is the diagnosis, and what may be found on urinalysis? | Multiple myeloma (plasma cell neoplasm); Bence Jones protein (Ig light chains). |
| ■ AIDS patient has just been diagnosed with cancer. | What neoplasms are associated with AIDS? | B-cell lymphoma, Kaposi's sarcoma. |
| ■ Patient with a new cancer diagnosis and known history of CHF is being evaluated for chemotherapy. | What chemotherapeutic agent should be avoided in this patient? | Doxorubicin (cardiotoxic). |
| ■ Chromosome analysis reveals the presence of the Philadelphia chromosome, t(9;22). | What is the latest targeted therapy for this disease, and how does it work? | Imatinib (Gleevec) is used to treat CML; monoclonal antibody against the <i>bcr-abl</i> tyrosine kinase. |

Blood cell differentiation



Erythrocyte



Anucleate, biconcave → large surface area: volume ratio → easy gas exchange (O_2 and CO_2). Source of energy—glucose (90% anaerobically degraded to lactate, 10% by HMP shunt). Survival time—120 days. Membrane contains the chloride-bicarbonate antiport important in the “physiologic chloride shift,” which allows the RBC to transport CO_2 from the periphery to the lungs for elimination.

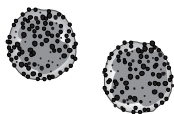
Eryth = red; *cyte* = cell.
 Erythrocytosis = polycythemia = ↑ number of red cells.
 Anisocytosis = varying sizes.
 Poikilocytosis = varying shapes.
 Reticulocyte = immature erythrocyte.

Leukocyte

Types: granulocytes (basophils, eosinophils, neutrophils) and mononuclear cells (lymphocytes, monocytes). Responsible for defense against infections. Normally 4000–10,000 per microliter.

Leuk = white; *cyte* = cell.

Basophil



Mediates allergic reaction. < 1% of all leukocytes. Bilobate nucleus. Densely basophilic granules containing heparin (anticoagulant), histamine (vasodilator) and other vasoactive amines, and leukotrienes (LTD-4). Found in the blood.

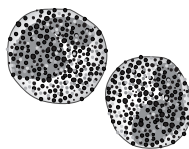
Basophilic—staining readily with **basic** stains.

Mast cell



Mediates allergic reaction. Degranulation—histamine, heparin, and eosinophil chemotactic release of factors. Can bind IgE to membrane. Mast cells resemble basophils structurally and functionally but are not the same cell type. Found in tissue.

Involved in type I hypersensitivity reactions. Cromolyn sodium prevents mast cell degranulation (used to treat asthma).

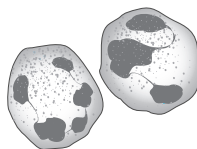
► HEMATOLOGY AND ONCOLOGY—ANATOMY (*continued*)**Eosinophil**

1–6% of all leukocytes. Bilobate nucleus. Packed with large eosinophilic granules of uniform size. Defends against helminthic and protozoan infections (major basic protein). Highly phagocytic for antigen-antibody complexes. Produces histaminase and arylsulfatase.

Eosin = a dye; *philic* = loving.
Causes of eosinophilia =

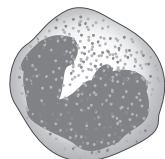
NAACP:

- Neoplastic
- Asthma
- Allergic processes
- Collagen vascular diseases
- Parasites

Neutrophil

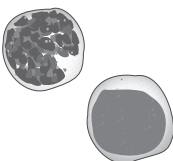
Acute inflammatory response cell. 40–75% WBCs. Phagocytic. Multilobed nucleus. Large, spherical, azurophilic 1° granules (called lysosomes) contain hydrolytic enzymes, lysozyme, myeloperoxidase, and lactoferrin.

Hypersegmented polys are seen in vitamin B₁₂/folate deficiency.

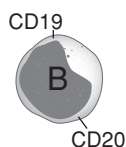
Monocyte

2–10% of leukocytes. Large. Kidney-shaped nucleus. Extensive “frosted glass” cytoplasm. Differentiates into macrophages in tissues.

Mono = one, single; *cyte* = cell.

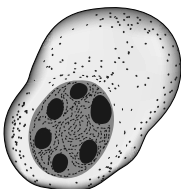
Lymphocyte

Small. Round, densely staining nucleus. Small amount of pale cytoplasm. B lymphocytes produce antibodies. T lymphocytes manifest the cellular immune response as well as regulate B lymphocytes and macrophages.

B lymphocyte

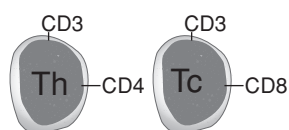
Part of humoral immune response. Arises from stem cells in bone marrow. Matures in marrow. Migrates to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells and produce antibodies. Has memory. Can function as antigen-presenting cell (APC) via MHC II.

B = Bone marrow.

Plasma cell

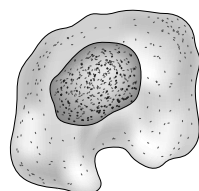
Off-center nucleus, clock-face chromatin distribution, abundant RER and well-developed Golgi apparatus. B cells differentiate into plasma cells, which can produce large amounts of antibody specific to a particular antigen.

Multiple myeloma is a plasma cell neoplasm.

T lymphocyte

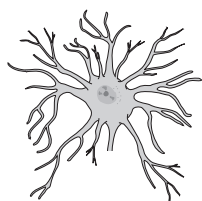
Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (MHC I, CD8), helper T cells (MHC II, CD4), and suppressor T cells.

T is for Thymus. CD is for Cluster of Differentiation. $\text{MHC} \times \text{CD} = 8$ (e.g., MHC 2 \times CD4 = 8, and MHC 1 \times CD8 = 8).

Macrophage

Phagocytizes bacteria, cell debris, and senescent red cells and scavenges damaged cells and tissues. Long life in tissues. Macrophages differentiate from circulating blood monocytes. Activated by γ -interferon. Can function as APC via MHC II.

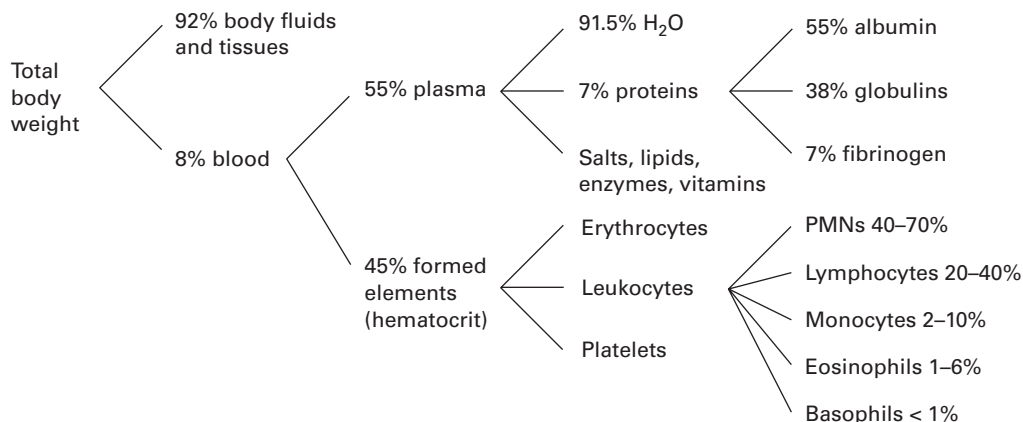
Macro = large; *phage* = eater.

Dendritic cells

Professional APCs. Express MHC II and Fc receptor (FcR) on surface. Main inducers of 1° antibody response. Called Langerhans cells on skin.

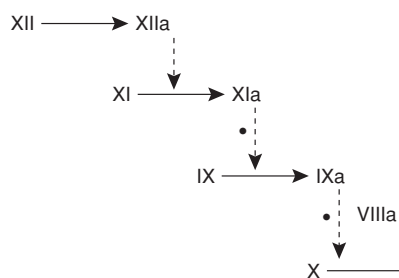
Blood composition

Normal adult blood composition. Note that serum = plasma – clotting factors (e.g., fibrinogen).



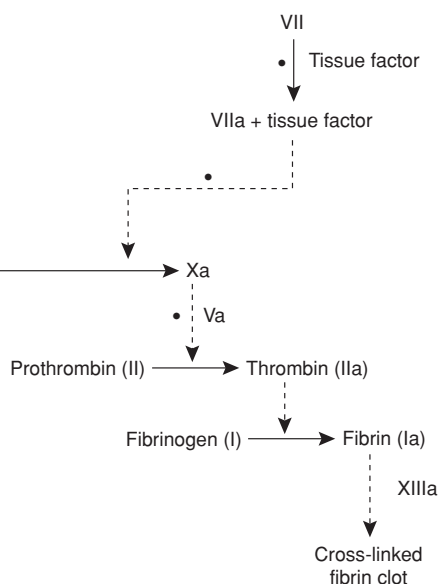
Coagulation cascade

Intrinsic pathway (PTT)



• Step requires Ca^{2+} and platelet phospholipid

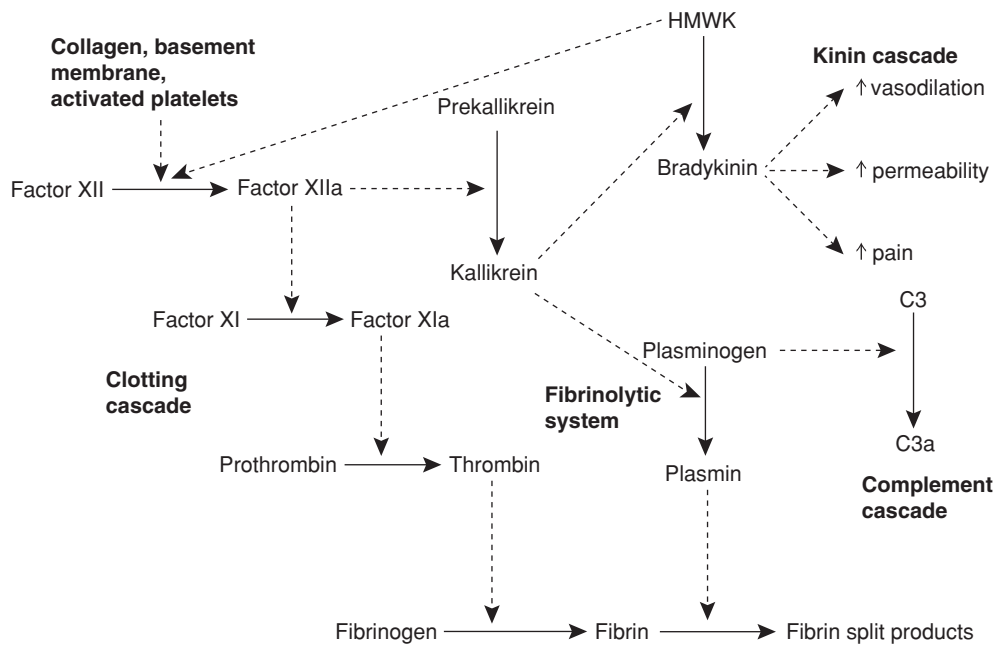
Extrinsic pathway (PT)



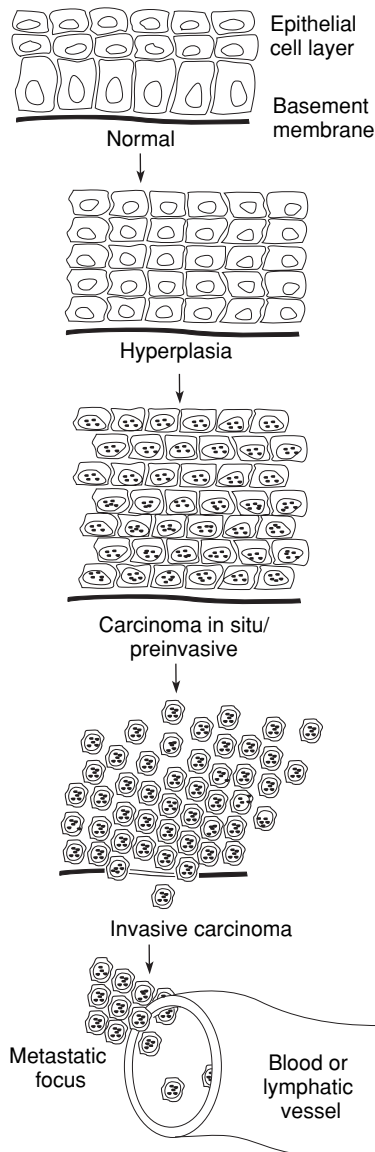
Coagulation factor inhibitors and fibrinolysis

Protein C and protein S—inactivate Va and VIIIa ; vitamin K–dependent.
 Antithrombin III—inactivates thrombin, IXa , Xa , and XIa ; activated by heparin.
 tPA—generates plasmin, which cleaves fibrin.

Convergence of coagulation, complement, and kinin pathways



Neoplastic progression



- Normal cells with basal → apical differentiation

- Cells have increased in number—**hyperplasia**
- Abnormal proliferation of cells with loss of size, shape, and orientation—**dysplasia**

- **In situ carcinoma**
- Neoplastic cells have not invaded basement membrane
- High nuclear/cytoplasmic ratio and clumped chromatin
- Neoplastic cells encompass entire thickness

- Cells have invaded basement membrane using **collagenases** and **hydrolases**
- Can metastasize if they reach a blood or lymphatic vessel

Metastasis—spread to distant organ

- Must survive immune attack
- "Seed and soil" theory of metastasis
 - Seed = tumor embolus
 - Soil = target organ—liver, lungs, bone, brain...

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:84.)

-plasia definitions

Hyperplasia—↑ in number of cells (reversible).

Metaplasia—1 adult cell type is replaced by another (reversible). Often 2° to irritation and/or environmental exposure (e.g., squamous metaplasia in trachea and bronchi of smokers).

Dysplasia—abnormal growth with loss of cellular orientation, shape, and size in comparison to normal tissue maturation; commonly preneoplastic (reversible).

Anaplasia—abnormal cells lacking differentiation; like primitive cells of same tissue, often equated with undifferentiated malignant neoplasms. Tumor giant cells may be formed.

Neoplasia—a clonal proliferation of cells that is uncontrolled and excessive.

Tumor grade vs. stage

Grade	Degree of cellular differentiation based on histologic appearance of tumor. Usually graded I–IV based on degree of differentiation and number of mitoses per high-power field; character of tumor itself.	Stage usually has more prognostic value than grade. Stage = Spread. TNM staging system: T = size of Tumor N = Node involvement M = Metastases
Stage	Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases; spread of tumor in a specific patient.	

Tumor nomenclature

Cell type	Benign	Malignant ^a
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
> 1 cell type	Mature teratoma	Immature teratoma

^aThe term **carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

Diseases associated with neoplasms	Condition	Neoplasm
	1. Down syndrome	1. ALL (we ALL fall Down), AML
	2. Xeroderma pigmentosum, albinism	2. Melanoma and basal, squamous cell carcinomas of skin
	3. Chronic atrophic gastritis, pernicious anemia, postsurgical gastric remnants	3. Gastric adenocarcinoma
	4. Tuberous sclerosis (facial angiofibroma, seizures, mental retardation)	4. Astrocytoma and cardiac rhabdomyoma
	5. Actinic keratosis	5. Squamous cell carcinoma of skin
	6. Barrett's esophagus (chronic GI reflux)	6. Esophageal adenocarcinoma
	7. Plummer-Vinson syndrome (atrophic glossitis, esophageal webs, anemia; all due to iron deficiency)	7. Squamous cell carcinoma of esophagus
	8. Cirrhosis (alcoholic, hepatitis B or C)	8. Hepatocellular carcinoma
	9. Ulcerative colitis	9. Colonic adenocarcinoma
	10. Paget's disease of bone	10. 2° osteosarcoma and fibrosarcoma
	11. Immunodeficiency states	11. Malignant lymphomas
	12. AIDS	12. Aggressive malignant lymphomas (non-Hodgkin's) and Kaposi's sarcoma
	13. Autoimmune diseases (e.g., Hashimoto's thyroiditis, myasthenia gravis)	13. Benign and malignant thymomas
	14. Acanthosis nigricans (hyperpigmentation and epidermal thickening)	14. Visceral malignancy (stomach, lung, breast, uterus)
	15. Dysplastic nevus	15. Malignant melanoma

Oncogenes	Gain of function → cancer.
Gene	Associated tumor
<i>abl</i>	CML
<i>c-myc</i>	Burkitt's lymphoma
<i>bcl-2</i>	Follicular and undifferentiated lymphomas (inhibits apoptosis)
<i>erb-B2</i>	Breast, ovarian, and gastric carcinomas
<i>ras</i>	Colon carcinoma
<i>L-myc</i>	Lung tumor
<i>N-myc</i>	Neuroblastoma
<i>ret</i>	Multiple endocrine neoplasia (MEN) types II and III

Tumor suppressor genes		Loss of function → cancer; both alleles must be lost for expression of disease.
Gene	Chromosome	Associated tumor
<i>Rb</i>	13q	Retinoblastoma, osteosarcoma
<i>BRCA1</i> and 2	17q, 13q	Breast and ovarian cancer
<i>p53</i>	17p	Most human cancers, Li-Fraumeni syndrome
<i>p16</i>	9p	Melanoma
<i>APC</i>	5q	Colorectal cancer
<i>WT1</i>	11q	Wilms' tumor
<i>NF1</i>	17q	Neurofibromatosis type 1
<i>NF2</i>	22q	Neurofibromatosis type 2
<i>DPC</i>	18q	Pancreatic cancer
<i>DCC</i>	18q	Colon cancer

Tumor markers		
PSA (prostatic acid phosphatase)	Prostate-specific antigen. Prostatic carcinoma. Used for screening.	Tumor markers should not be used as the 1° tool for cancer diagnosis. They may be used to confirm diagnosis, to monitor for tumor recurrence, and to monitor response to therapy.
CEA	Carcinoembryonic antigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric and breast carcinomas.	
α-fetoprotein	Normally made by fetus. Hepatocellular carcinomas. Nonseminomatous germ cell tumors of the testis (e.g., yolk sac tumor).	
β-hCG	Hydatidiform moles, Choriocarcinomas, and Gestational trophoblastic tumors.	
CA-125	Ovarian, malignant epithelial tumors.	
S-100	Melanoma, neural tumors, astrocytomas.	
Alkaline phosphatase	Metastases to bone, obstructive biliary disease, Paget's disease of bone.	
Bombesin	Neuroblastoma, lung and gastric cancer.	
TRAP	Tartrate-resistant acid phosphatase. Hairy cell leukemia—a B-cell neoplasm.	

Psammoma bodies	Laminated, concentric, calcific spherules seen in: 1. Papillary adenocarcinoma of thyroid 2. Serous papillary cystadenocarcinoma of ovary 3. Meningioma 4. Malignant mesothelioma	PSaMMoma: Papillary (thyroid) Serous (ovary) Meningioma Mesothelioma
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Oncogenic viruses	Virus	Associated cancer
	HTLV-1	Adult T-cell leukemia
	HBV, HCV	Hepatocellular carcinoma
	EBV	Burkitt's lymphoma, nasopharyngeal carcinoma
	HPV	Cervical carcinoma (16, 18), penile/anal carcinoma
	HHV-8 (Kaposi's sarcoma-associated herpesvirus)	Kaposi's sarcoma, body cavity fluid B-cell lymphoma

Chemical carcinogens	Toxin	Affected organ
	Aflatoxins	Liver (hepatocellular carcinoma)
	Vinyl chloride	Liver (angiosarcoma)
	CCl ₄	Liver (centrilobular necrosis, fatty change)
	Nitrosamines	Esophagus, stomach
	Cigarette smoke	Larynx, lung
	Asbestos	Lung (mesothelioma and bronchogenic carcinoma)
	Arsenic	Skin (squamous cell carcinoma)
	Naphthalene (aniline) dyes	Bladder (transitional cell carcinoma)
	Alkylating agents	Blood (leukemia)

Paraneoplastic effects of tumors

Neoplasm	Causes	Effect
Small cell lung carcinoma	ACTH or ACTH-like peptide	Cushing's syndrome
Small cell lung carcinoma and intracranial neoplasms	ADH	SIADH
Squamous cell lung carcinoma, renal cell carcinoma, breast carcinoma, multiple myeloma, and bone metastasis (lysed bone)	PTH-related peptide, TGF- β , TNF- α , IL-1	Hypercalcemia
Renal cell carcinoma, hemangioblastoma	Erythropoietin	Polycythemia
Thymoma, small cell lung carcinoma	Antibodies against presynaptic Ca ²⁺ channels at neuromuscular junction	Lambert-Eaton syndrome (muscle weakness)
Leukemias and lymphomas	Hyperuricemia due to excess nucleic acid turnover (i.e., cytotoxic therapy)	Gout, urate nephropathy

Metastasis to brain	1° tumors that metastasize to brain—Lung, Breast, Skin (melanoma), Kidney (renal cell carcinoma), GI. Overall, approximately 50% of brain tumors are from metastases.	Lots of Bad Stuff Kills Glia. Typically multiple well-circumscribed tumors at gray-white border.
Metastasis to liver	The liver and lung are the most common sites of metastasis after the regional lymph nodes. 1° tumors that metastasize to the liver—Colon > Stomach > Pancreas > Breast > Lung.	Metastases >> 1° liver tumors. Cancer Sometimes Penetrates Benign Liver.
Metastasis to bone	These 1° tumors metastasize to bone—Prostate, Thyroid, Testes, Breast, Lung, Kidney. Metastases from breast and prostate are most common. Metastatic bone tumors are far more common than 1° bone tumors.	P. T. Barnum Loves Kids. Lung = Lytic. Prostate = blastic. Breast = Both lytic and blastic.

Cancer epidemiology

	Male	Female	
Incidence	Prostate (32%) Lung (16%) Colon and rectum (12%)	Breast (32%) Lung (13%) Colon and rectum (13%)	Deaths from lung cancer have plateaued in males but continue to ↑ in females.
Mortality	Lung (33%) Prostate (13%)	Lung (23%) Breast (18%)	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

RBC forms

Biconcave	Normal.	
Spherocytes	Hereditary spherocytosis, autoimmune hemolysis.	
Elliptocyte	Hereditary elliptocytosis.	
Macro-ovalocyte	Megaloblastic anemia (also hypersegmented PMNs), marrow failure.	
Helmet cell, schistocyte	DIC, traumatic hemolysis.	
Sickle cell	Sickle cell anemia.	
Teardrop cell	Myeloid metaplasia with myelofibrosis.	
Acanthocyte	Spiny appearance in abetalipoproteinemia.	
Target cell	HbC disease, Asplenia, Liver disease, Thalassemia.	HALT.
Poikilocytes	Nonuniform shapes in TTP/HUS, microvascular damage, DIC.	
Burr cell	TTP/HUS.	

Anemia

Type

Microcytic,
hypochromic
(MCV < 80)

Macrocytic
(MCV > 100)

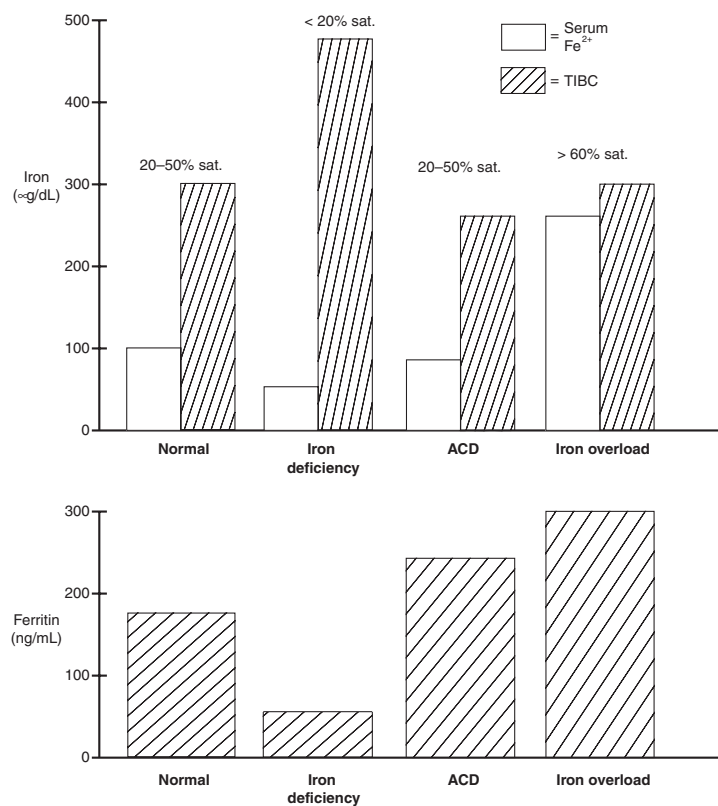
Normocytic,
normochromic

Etiology

Iron deficiency—↓ serum iron, ↑ TIBC, ↓ ferritin
(see Color Image 20)
Thalassemias—target cells (see Color Image 18)
Lead poisoning, sideroblastic anemias
Megaloblastic—vitamin B₁₂/folate deficiency
Drugs that block DNA synthesis (e.g., sulfa drugs, AZT)
Marked reticulocytosis (bigger than mature RBCs)
Acute hemorrhage
Enzyme defects (e.g., G6PD deficiency, PK deficiency)
RBC membrane defects (e.g., hereditary spherocytosis)
Bone marrow disorders (e.g., aplastic anemia, leukemia)
Hemoglobinopathies (e.g., sickle cell disease)
Autoimmune hemolytic anemia
Anemia of chronic disease (ACD)—↓ TIBC, ↑ ferritin,
↑ storage iron in marrow macrophages

Comments

Vitamin B₁₂ and folate deficiencies are associated with hypersegmented PMNs. Unlike folate deficiency, vitamin B₁₂ deficiency (e.g., pernicious anemia) is associated with neurologic problems.
↓ serum haptoglobin and ↑ serum LDH indicate RBC hemolysis. Direct Coombs' test is used to distinguish between immune- vs. non-immune-mediated RBC hemolysis.



Aplastic anemia	Pancytopenia characterized by severe anemia, neutropenia, and thrombocytopenia caused by failure or destruction of multipotent myeloid stem cells, with inadequate production or release of differentiated cell lines.	
Causes	Radiation, benzene, chloramphenicol, alkylating agents, antimetabolites, viral agents (parvovirus B19, EBV, HIV), Fanconi's anemia, idiopathic (immune-mediated, 1° stem-cell defect). May follow acute hepatitis.	
Symptoms	Fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection.	
Pathologic features	Pancytopenia with normal cell morphology; hypocellular bone marrow with fatty infiltration. Diagnose with bone marrow biopsy.	
Treatment	Withdrawal of offending agent, allogenic bone marrow transplantation, RBC and platelet transfusion, G-CSF or GM-CSF.	

Blood dyscrasias		
Sickle cell anemia	<p>HbS mutation is a single amino acid replacement in β chain (substitution of normal glutamic acid with valine). Low O_2 or dehydration precipitates sickling. Heterozygotes (sickle cell trait) are relatively malaria resistant (balanced polymorphism). Complications in homozygotes (sickle cell disease) include aplastic crisis (due to parvovirus B19 infection), autosplenectomy, \uparrow risk of encapsulated organism infection, <i>Salmonella</i> osteomyelitis, painful crisis (vaso-occlusive), and splenic sequestration crisis (see Color Image 21). New therapies for sickle cell anemia include hydroxyurea (\uparrow HbF) and bone marrow transplantation.</p> <p>HbC defect is a different β-chain mutation; patients with HbC or HbSC (1 of each mutant gene) have milder disease than do HbSS patients.</p>	<p>8% of African-Americans carry the HbS trait; 0.2% have the disease.</p> <p>Sickled cells are crescent-shaped RBCs.</p> <p>“Crew cut” on skull x-ray due to marrow expansion from \uparrow erythropoiesis (also in thalassemias).</p>
α -thalassemia	<p>There are 4 α-globin genes. In α-thalassemia, the α-globin chain is underproduced (as a function of number of bad genes, 1–4). There is no compensatory \uparrow of any other chains. HbH (β_4-tetramers, lacks 3 α-globin genes). Hb Barts (γ_4-tetramers, lacks all 4 α-globin genes) results in hydrops fetalis and intrauterine fetal death.</p>	<p>α-thalassemia is prevalent in Asia and Africa. β-thalassemia is prevalent in Mediterranean populations.</p>
β -thalassemia	<p>In β-thalassemia minor (heterozygote), the β chain is underproduced; in β-thalassemia major (homozygote), the β chain is absent. In both cases, fetal hemoglobin production is compensatorily \uparrow but is inadequate. HbS/β-thalassemia heterozygote has mild to moderate disease (see Color Image 19).</p>	<p>β-thalassemia major results in severe anemia requiring blood transfusions. Cardiac failure due to 2° hemochromatosis. Marrow expansion \rightarrow skeletal deformities.</p>

Hemolytic anemias	↑ serum bilirubin (jaundice, pigment gallstones), ↑ reticulocytes (marrow compensating for anemia).	
Autoimmune anemia	<p>Mostly extravascular hemolysis (accelerated RBC destruction in liver Kupffer cells and spleen).</p> <p>Warm agglutinin (IgG)—chronic anemia seen in SLE, in CLL, or with certain drugs (e.g., α-methyl dopa).</p> <p>Cold agglutinin (IgM)—acute anemia triggered by cold; seen during recovery from <i>Mycoplasma pneumoniae</i> or infectious mononucleosis.</p> <p>Erythroblastosis fetalis—seen in newborn due to Rh or other blood antigen incompatibility → mother's antibodies attack fetal RBCs.</p>	<p>Autoimmune hemolytic anemias are Coombs positive.</p> <p>Direct Coombs' test: anti-Ig Ab added to patient's RBCs agglutinate if RBCs are coated with Ig.</p> <p>Indirect Coombs' test: normal RBCs added to patient's serum agglutinate if serum has anti-RBC surface Ig.</p> <p>Warm weather is GGGreat.</p> <p>Cold ice cream . . . MMM.</p> <p>Coombs negative. Osmotic fragility test used to confirm.</p>
Hereditary spherocytosis	Intrinsic, extravascular hemolysis due to spectrin or ankyrin defect. RBCs are small and round with no central pallor → less membrane → ↑ MCHC, ↑ RDW.	
Paroxysmal nocturnal hemoglobinuria	Intravascular hemolysis due to membrane defect → ↑ sensitivity of RBCs to the lytic activity of complement.	↑ urine hemosiderin.
Microangiopathic anemia	Intravascular hemolysis seen in DIC, TTP/HUS, SLE, or malignant hypertension.	Schistocytes (helmet cells) seen on blood smear.
DIC	Activation of coagulation cascade leading to microthrombi and global consumption of platelets, fibrin, and coagulation factors.	
Causes	Obstetric complications (most common cause), gram-negative sepsis, transfusion, trauma, malignancy, acute pancreatitis, nephrotic syndrome.	
Lab findings	↑ PT, ↑ PTT, ↑ fibrin split products (D-dimers), ↓ platelet count. Helmet-shaped cells and schistocytes on blood smear.	
Bleeding disorders		
Platelet abnormalities	<p>Causes include:</p> <ol style="list-style-type: none"> 1. ITP (antiplatelet antibodies, ↑ megakaryocytes) 2. TTP (schistocytes, ↑ LDH, neurologic symptoms) 3. DIC (schistocytes, ↑ fibrin split products) 4. Aplastic anemia 5. Drugs (e.g., immunosuppressive agents) 	Microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time.
Coagulation factor defects	<p>Coagulopathies include:</p> <ol style="list-style-type: none"> 1. Hemophilia A (factor VIII deficiency) 2. Hemophilia B (factor IX deficiency) 3. von Willebrand's disease (mild; most common bleeding disorder; deficiency of von Willebrand factor → defect of platelet adhesion and ↓ factor VIII survival) 	Macrohemorrhage: hemarthroses (bleeding into joints), easy bruising, ↑ PT and/or PTT.

Hemorrhagic disorders

Disorder	Platelet count ^b	Bleeding time	PT ^c	PTT ^d
Qualitative platelet defects ^a	—	↑	—	—
Thrombocytopenia	↓	↑	—	—
Hemophilia A or B	—	—	—	↑
von Willebrand's disease	—	↑	—	↑
DIC	↓	↑	↑	↑

^aBernard-Soulier disease = defect of platelet adhesion (↓ GP Ib); Glanzmann's thrombasthenia = defect of platelet aggregation (↓ GP IIb-IIIa).

^bNote: platelet count must reach a very low value (15,000–20,000/mm³) before generalized bleeding occurs; thrombocytopenia = < 100,000/mm³.

^cPT (extrinsic)—factors II, V, VII, and X.

^dPTT (intrinsic)—all factors except VII.

Lymphomas

Hodgkin's

Presence of Reed-Sternberg cells (RS cells are CD30⁺ and CD15⁺ B-cell origin) (see Color Image 25)
 Localized, single group of nodes; extranodal rare; contiguous spread
 Constitutional ("B") signs/symptoms—low-grade fever, night sweats, weight loss
 Mediastinal lymphadenopathy
 50% of cases associated with EBV; bimodal distribution—young and old; more common in men except for nodular sclerosing type
 Good prognosis = ↑ lymphocytes, ↓ RS

Non-Hodgkin's

Associated with HIV and immunosuppression
 Multiple, peripheral nodes; extranodal involvement common; noncontiguous spread
 Majority involve B cells (except those of lymphoblastic T-cell origin)
 No hypergammaglobulinemia
 Fewer constitutional signs/symptoms
 Peak incidence 20–40 years old

Hodgkin's lymphoma

Type	RS	Lymphos	Prognosis	Comments
Nodular sclerosing (65–75%)	+	+++	Excellent	Most common; collagen banding; lacunar cells; women > men; primarily young adults.
Mixed cellularity (25%)	++++	+++	Intermediate	Numerous RS cells.
Lymphocyte predominant (6%)	+	++++	Excellent	< 35-year-old males.
Lymphocyte depleted (rare)	*	+	Poor	Older males with disseminated disease.

*RS high relative to lymphocytes

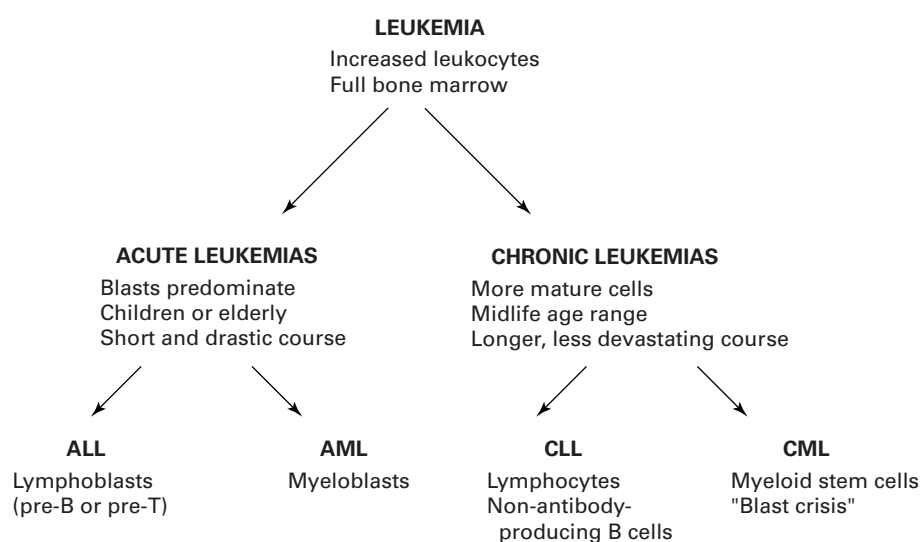
Reed-Sternberg cells

Distinctive tumor giant cell seen in Hodgkin's disease; binucleate or bilobed with the 2 halves as mirror images ("owl's eyes"). Necessary but not sufficient for a diagnosis of Hodgkin's disease. Variants include lacunar cells in nodular sclerosis variant.

Non-Hodgkin's lymphoma

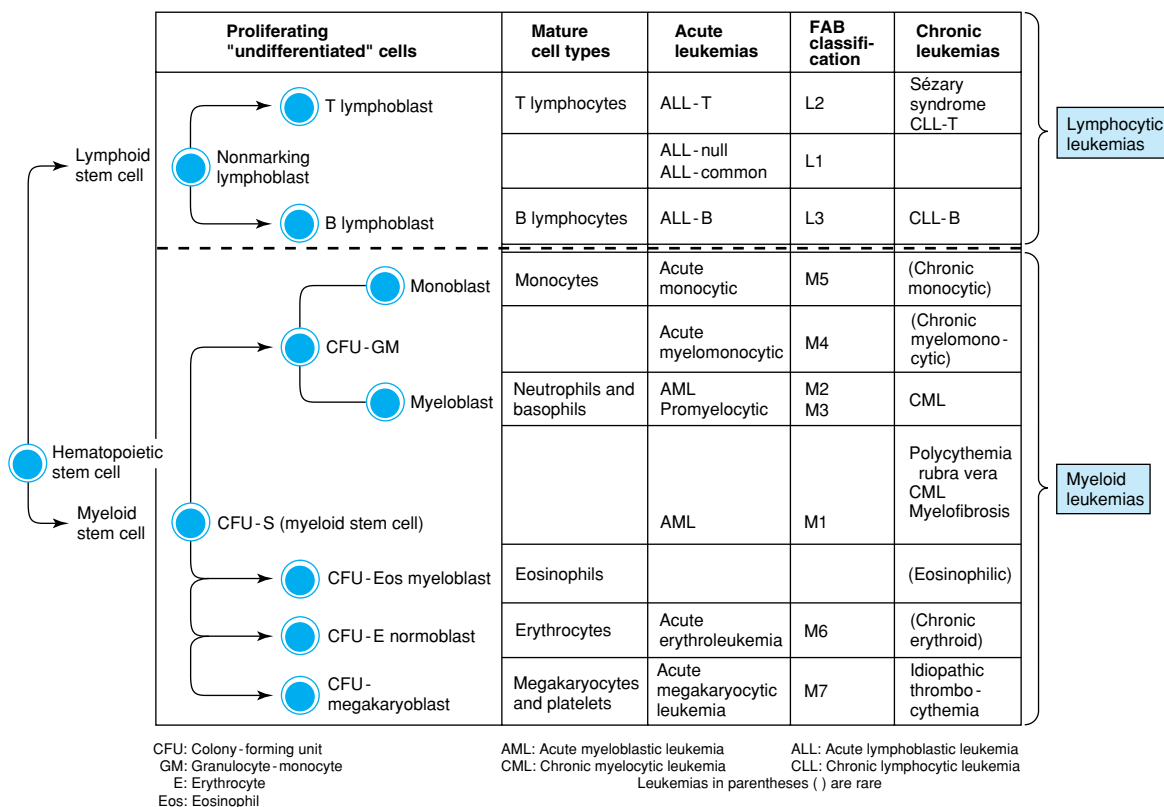
Type	Occurs in	Cell type	Genetics	Comments
Small lymphocytic lymphoma	Adults	B cells		Like CLL with focal mass; low grade.
Follicular lymphoma (small cleaved cell)	Adults	B cells	t(14;18) <i>bcl-2</i> expression	Most common (adult). Difficult to cure; indolent course; <i>bcl-2</i> is involved in apoptosis.
Diffuse large cell	Usually older adults, but 20% occur in children	80% B cells 20% T cells (mature)		Aggressive, but up to 50% are curable.
Lymphoblastic lymphoma	Most often children	T cells (immature)		Most common in children; commonly presents with ALL and mediastinal mass; very aggressive T-cell lymphoma.
Burkitt's lymphoma	Most often children	B cells	t(8;14) <i>c-myc</i> gene moves next to heavy-chain Ig gene (14)	"Starry-sky" appearance (sheets of lymphocytes with interspersed macrophages); associated with EBV; jaw lesion in endemic form in Africa; pelvis or abdomen in sporadic form (see Color Image 24).

Leukemias	General considerations—↑ number of circulating leukocytes in blood; bone marrow infiltrates of leukemic cells; marrow failure can cause anemia (↓ RBCs), infections (↓ WBCs), and hemorrhage (↓ platelets); leukemic cell infiltrates in liver, spleen, and lymph nodes are common (see Color Image 22).
ALL	Children; lymphoblasts; most responsive to therapy. May spread to CNS and testes.
AML	Auer rods; myeloblasts; adults.
CLL	Older adults; lymphadenopathy; hepatosplenomegaly; few symptoms; indolent course; ↑ smudge cells in peripheral blood smear; warm antibody autoimmune hemolytic anemia; very similar to SLL (small lymphocytic lymphoma).
CML	Most commonly associated with Philadelphia chromosome (t[9;22], <i>bcr-abl</i>); myeloid stem cell proliferation; presents with ↑ neutrophils and metamyelocytes; splenomegaly; may accelerate to AML (“blast crisis”). Very low leukocyte alkaline phosphatase (vs. leukemoid reaction).



Auer bodies (rods)	Auer rods are peroxidase-positive cytoplasmic inclusions in granulocytes and myeloblasts. Primarily seen in acute promyelocytic leukemia (M3). Treatment of AML M3 can release Auer rods → DIC.
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Leukemia classification

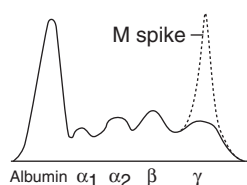


(Adapted, with permission, from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:410.)

Chromosomal translocations

Translocation	Associated disorder
t(9;22) (Philadelphia chromosome)	CML (<i>bcr-abl</i> hybrid)
t(8;14)	Burkitt's lymphoma (<i>c-myc</i> activation)
t(14;18)	Follicular lymphomas (<i>bcl-2</i> activation)
t(15;17)	M3 type of AML (responsive to all- <i>trans</i> retinoic acid)
t(11;22)	Ewing's sarcoma
t(11;14)	Mantle cell lymphoma

Multiple myeloma



(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:806.)

Monoclonal plasma cell ("fried-egg" appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Most common 1° tumor arising within bone in adults. Destructive bone lesions and consequent hypercalcemia. Renal insufficiency, ↑ susceptibility to infection, and anemia. Associated with 1° amyloidosis and punched-out lytic bone lesions on x-ray. Characterized by monoclonal immunoglobulin spike (M protein) on serum protein electrophoresis and Ig light chains in urine (Bence Jones protein). Blood smear shows RBCs stacked like poker chips (rouleau formation). Compare with Waldenström's macroglobulinemia → M spike = IgM (→ hyperviscosity symptoms); no lytic bone lesions (see Color Image 23).

Heparin

Mechanism	Catalyzes the activation of antithrombin III, ↓ thrombin and Xa. Short half-life.
Clinical use	Immediate anticoagulation for pulmonary embolism, stroke, angina, MI, DVT. Used during pregnancy (does not cross placenta). Follow PTT.
Toxicity	Bleeding, thrombocytopenia, drug-drug interactions. For rapid reversal of heparinization, use protamine sulfate (positively charged molecule that acts by binding negatively charged heparin).
Note	Newer low-molecular-weight heparins (enoxaparin) act more on Xa, have better bioavailability and 2–4 times longer half-life. Can be administered subcutaneously and without laboratory monitoring. Not easily reversible.

Warfarin (Coumadin)

Mechanism	Interferes with normal synthesis and γ -carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X and protein C and S. Affects EX trinsic pathway and ↑ PT . Long half-life.	The EX - Pa Triot went to WAR (farin).
Clinical use	Chronic anticoagulation. Not used in pregnant women (because warfarin, unlike heparin, can cross the placenta). Follow PT values.	
Toxicity	Bleeding, teratogenic, drug-drug interactions.	

Heparin vs. warfarin

	Heparin	Warfarin
Structure	Large anionic polymer, acidic	Small lipid-soluble molecule
Route of administration	Parenteral (IV, SC)	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
Mechanism of action	Activates antithrombin III, which ↓ the action of IIa (thrombin) and Xa	Impairs the synthesis of vitamin K–dependent clotting factors II, VII, IX, and X (vitamin K antagonist)
Duration of action	Acute (hours)	Chronic (weeks or months)
Inhibits coagulation in vitro	Yes	No
Treatment of acute overdose	Protamine sulfate	IV vitamin K and fresh frozen plasma
Monitoring	PTT (intrinsic pathway)	PT (extrinsic pathway)
Crosses placenta	No	Yes (teratogenic)

Thrombolytics

Mechanism

Clinical use

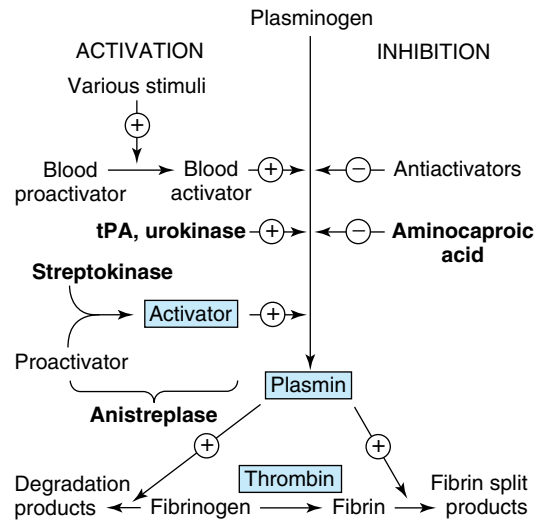
Toxicity

Streptokinase, urokinase, tPA (alteplase), APSAC (anistreplase).

Directly or indirectly aid conversion of plasminogen to plasmin, the major fibrinolytic enzyme, which cleaves thrombin and fibrin clots.

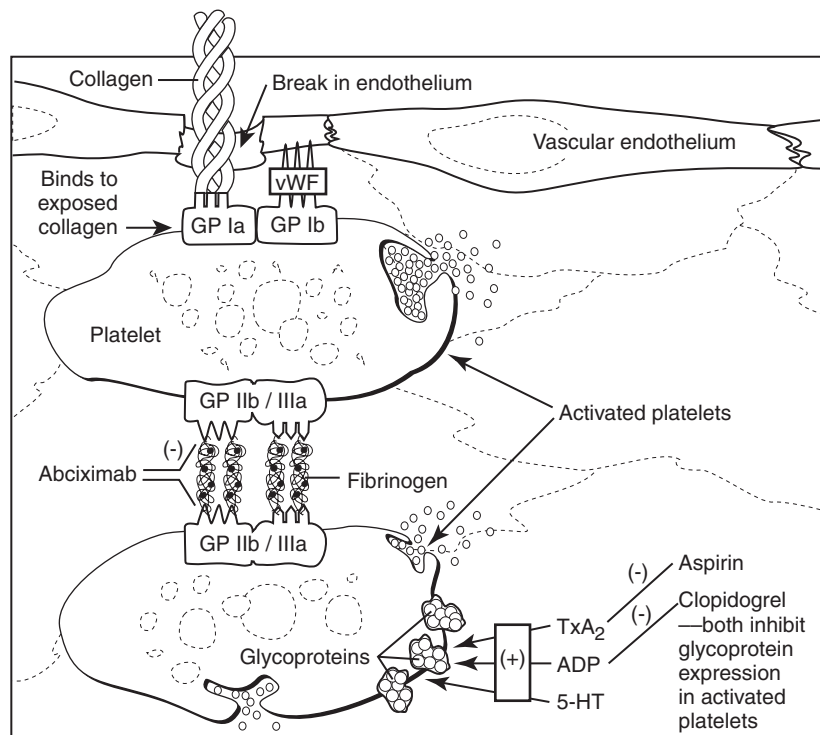
Early MI, early ischemic stroke.

Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diathesis, or severe hypertension. Treat toxicity with aminocaproic acid, an inhibitor of fibrinolysis.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:550.)

Mechanism of antiplatelet interaction



Aspirin (ASA)

Mechanism	Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to prostaglandins. ↑ bleeding time. No effect on PT, PTT.
Clinical use	Antipyretic, analgesic, anti-inflammatory, antiplatelet drug.
Toxicity	Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus (CN VIII).

Clopidogrel, ticlopidine

Mechanism	Inhibit platelet aggregation by irreversibly blocking ADP receptors. Inhibit fibrinogen binding by preventing glycoprotein IIb/IIIa expression.
Clinical use	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
Toxicity	Neutropenia (ticlopidine).

Abciximab

Mechanism	Monoclonal antibody that binds to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation.
Clinical use	Acute coronary syndromes, percutaneous transluminal coronary angioplasty.
Toxicity	Bleeding, thrombocytopenia.

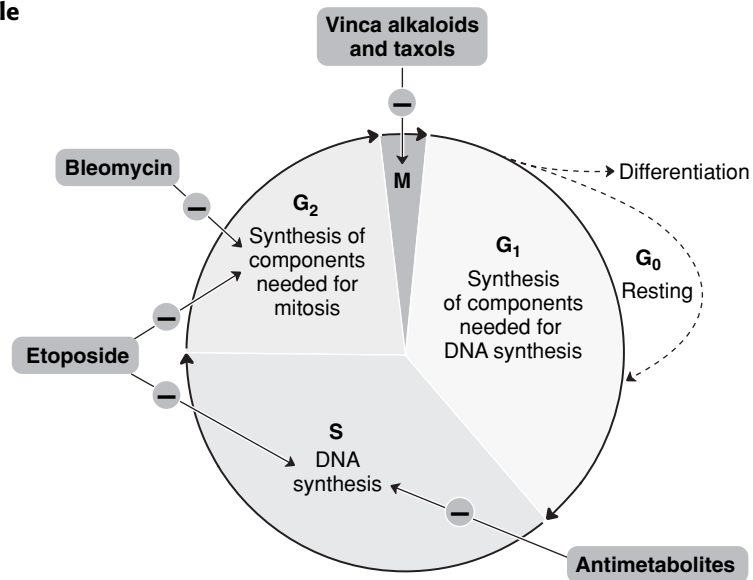
Cancer drugs—site of action**Nucleotide synthesis****DNA****mRNA****Protein**

1. Methotrexate + 5-FU—↓ thymidine synthesis
2. 6-MP—↓ purine synthesis
3. Cytarabine
4. Alkylating agents + cisplatin—DNA cross-linkage
5. Dactinomycin + doxorubicin—DNA intercalation
6. Bleomycin—strand breakage + DNA intercalation
7. Etoposide—strand breakage
8. Steroids
9. Tamoxifen
10. Vinca alkaloids—inhibit microtubule formation
11. Paclitaxel—inhibits microtubule disassembly

Cell cycle specific—
antimetabolites (MTX, 5-FU, 6-MP), etoposide, bleomycin, vinca alkaloids, paclitaxel.

Cell cycle nonspecific—
alkylating agents, antibiotics (dactinomycin, doxorubicin, bleomycin).

Cancer drugs—cell cycle



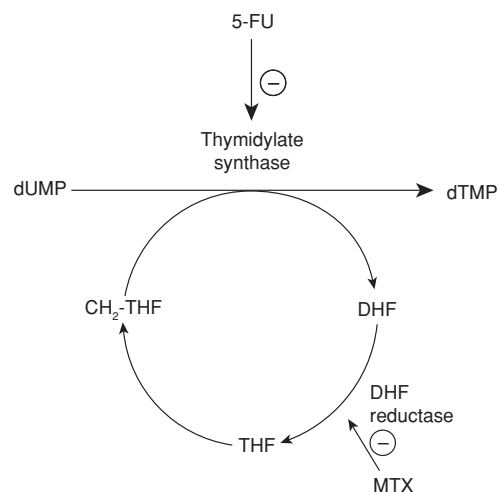
(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:133.)

Methotrexate (MTX)

Mechanism	S-phase-specific antimetabolite. Folic acid analog that inhibits dihydrofolate reductase, resulting in ↓ dTMP and therefore ↓ DNA and protein synthesis.
Clinical use	Leukemias, lymphomas, choriocarcinoma, sarcomas. Abortion, ectopic pregnancy, rheumatoid arthritis, psoriasis.
Toxicity	Myelosuppression, which is reversible with leucovorin (folinic acid) "rescue." Macrovesicular fatty change in liver.

5-fluorouracil (5-FU)

Mechanism	S-phase-specific antimetabolite. Pyrimidine analog bioactivated to 5F-dUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase, resulting in ↓ dTMP and same effects as MTX.
Clinical use	Colon cancer and other solid tumors, basal cell carcinoma (topical). Synergy with MTX.
Toxicity	Myelosuppression, which is NOT reversible with leucovorin; photosensitivity.



6-mercaptopurine (6-MP)

Mechanism	Blocks de novo purine synthesis. Activated by HGPRTase.
Clinical use	Leukemias, lymphomas (not CLL or Hodgkin's).
Toxicity	Bone marrow, GI, liver. Metabolized by xanthine oxidase; thus ↑ toxicity with allopurinol.

Cytarabine (ara-C)

Mechanism	Inhibits DNA polymerase.
Clinical use	AML.
Toxicity	Leukopenia, thrombocytopenia, megaloblastic anemia.

Cyclophosphamide, ifosfamide

Mechanism	Alkylating agents; covalently x-link (interstrand) DNA at guanine N-7. Require bioactivation by liver.
Clinical use	Non-Hodgkin's lymphoma, breast and ovarian carcinomas. Also immunosuppressants.
Toxicity	Myelosuppression; hemorrhagic cystitis, which can be partially prevented with mesna.

Nitrosoureas

Mechanism	Carmustine, lomustine, semustine, streptozocin.
Clinical use	Alkylate DNA. Require bioactivation. Cross blood-brain barrier → CNS.
Toxicity	Brain tumors (including glioblastoma multiforme). CNS toxicity (dizziness, ataxia).

Cisplatin, carboplatin

Mechanism	Act like alkylating agents.
Clinical use	Testicular, bladder, ovary, and lung carcinomas.
Toxicity	Nephrotoxicity and acoustic nerve damage.

Busulfan

Mechanism	Alkylates DNA.
Clinical use	CML.
Toxicity	Pulmonary fibrosis, hyperpigmentation.

Doxorubicin (Adriamycin), daunorubicin

Mechanism	Generate free radicals and noncovalently intercalate in DNA (creating breaks in DNA strand to ↓ replication).
Clinical use	Part of the ABVD combination regimen for Hodgkin's and for myelomas, sarcomas, and solid tumors (breast, ovary, lung).
Toxicity	Cardiotoxicity; also myelosuppression and marked alopecia. Toxic extravasation.

Dactinomycin (actinomycin D)

Mechanism	Intercalates in DNA.	ACTinomycin D is used for childhood tumors (children ACT out).
Clinical use	Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma.	
Toxicity	Myelosuppression.	

Bleomycin

Mechanism	Induces formation of free radicals, which cause breaks in DNA strands.
Clinical use	Testicular cancer, lymphomas (part of the ABVD regimen for Hodgkin's).
Toxicity	Pulmonary fibrosis, skin changes, but minimal myelosuppression.

Etoposide (VP-16)

Mechanism	G ₂ -phase-specific agent that inhibits topoisomerase II and ↑ DNA degradation.
Clinical use	Small cell carcinoma of the lung and prostate, testicular carcinoma.
Toxicity	Myelosuppression, GI irritation, alopecia.

Prednisone

Mechanism	May trigger apoptosis. May even work on nondividing cells.
Clinical use	Most commonly used glucocorticoid in cancer chemotherapy. Used in CLL, Hodgkin's lymphomas (part of the MOPP regimen). Also an immunosuppressant used in autoimmune diseases.
Toxicity	Cushing-like symptoms; immunosuppression, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.

Tamoxifen, raloxifene

Mechanism	Estrogen receptor mixed agonist/antagonists ("SERMs") that block the binding of estrogen to estrogen receptor-positive cells.
Clinical use	Breast cancer. Also useful to prevent osteoporosis.
Toxicity	Tamoxifen may ↑ the risk of endometrial carcinoma via partial agonist effects; "hot flashes."

Trastuzumab (Herceptin)

Mechanism	Monoclonal antibody against HER-2 (<i>erb-B2</i>). Helps kill breast cancer cells that overexpress HER-2, possibly through antibody-dependent cytotoxicity.
Clinical use	Metastatic breast cancer.
Toxicity	Cardiotoxicity.

Imatinib (Gleevec)

Mechanism	Myoclonal antibody against the Philadelphia chromosome <i>bcr-abl</i> tyrosine kinase.
Clinical use	CML, GI stromal tumors.
Toxicity	Fluid retention.

Vincristine, vinblastine

Mechanism	M-phase-specific alkaloids that bind to tubulin and block polymerization of microtubules so that mitotic spindle cannot form.
Clinical use	Part of the MOPP (Oncovin [vincristine]) regimen for lymphoma, Wilms' tumor, choriocarcinoma.
Toxicity	Vincristine—neurotoxicity (areflexia, peripheral neuritis), paralytic ileus. VinBLASTine BLASTs Bone marrow (suppression).

Paclitaxel, other taxols

Mechanism	M-phase-specific agents that bind to tubulin and hyperstabilize polymerized microtubules so that mitotic spindle cannot break down (anaphase cannot occur).
Clinical use	Ovarian and breast carcinomas.
Toxicity	Myelosuppression and hypersensitivity.

Musculoskeletal and Connective Tissue

“I just use my muscles like a conversation piece, like someone walking a cheetah down 42nd Street.”

—Arnold Schwarzenegger

“There’s 215 bones in the human body. That’s one.”

—Sarah Connor in *Terminator 2: Judgment Day*

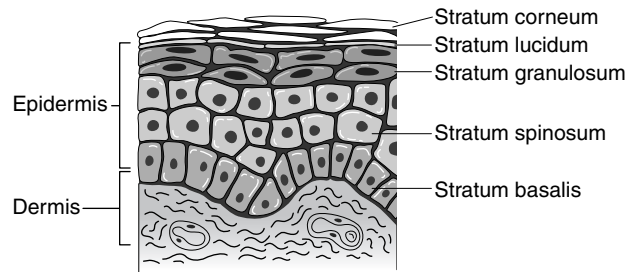
- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

■ Soccer player who was kicked in the leg suffered a damaged medial meniscus.	What else is likely to have been damaged?	Anterior cruciate ligament (remember the “unhappy triad”).
■ Gymnast dislocates her shoulder anteriorly.	What nerve is most likely to have been damaged?	Axillary nerve (C5, C6).
■ X-ray shows bilateral hilar lymphadenopathy.	What is the diagnosis?	Sarcoidosis.
■ Child exhibits weakness and enlarged calves.	What is the disease, and how it is inherited?	Duchenne’s muscular dystrophy; X-linked recessive.
■ 25-year-old woman presents with a low-grade fever, a rash across her nose that gets worse when she is out in the sun, and widespread edema.	You are concerned about what disease?	SLE.
■ 85-year-old man presents with acute knee pain and swelling. X-ray shows joint space without erosion.	What is the diagnosis, and what would you find on aspiration?	Pseudogout; rhomboid calcium pyrophosphate crystals.

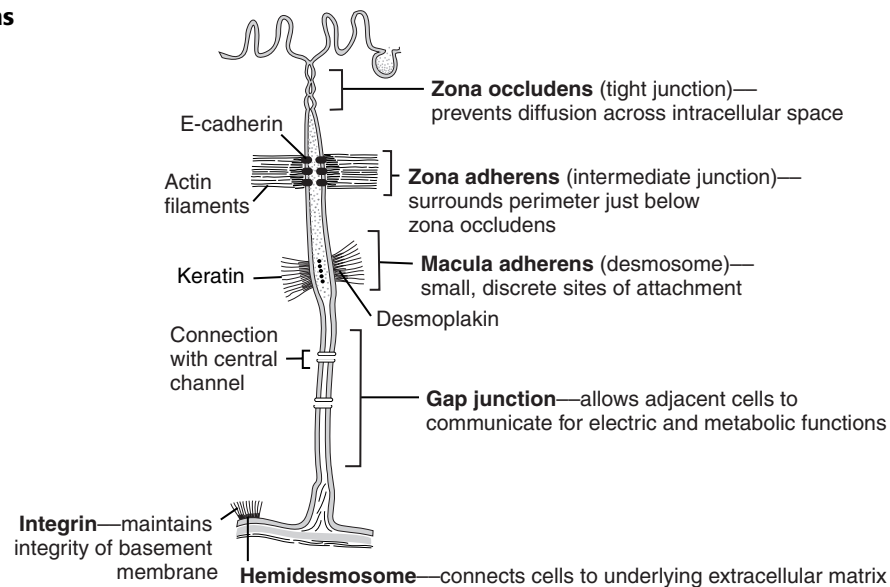
Epidermis layers

From surface to base: stratum Corneum, stratum Lucidum, stratum Granulosum, stratum Spinosum, stratum Basalis.

Californians Like Girls in String Bikinis.



Epithelial cell junctions

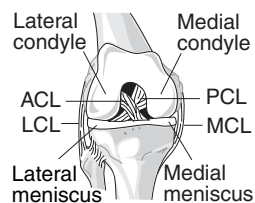


Bone formation

Intramembranous
Endochondral

Spontaneous bone formation without preexisting cartilage.
Ossification of cartilaginous molds. Long bones form by this type of ossification at 1° and 2° centers.

Unhappy triad/ knee injury



This common football injury (caused by clipping from the lateral side) consists of damage to medial collateral ligament (MCL), medial meniscus, and anterior cruciate ligament (ACL).

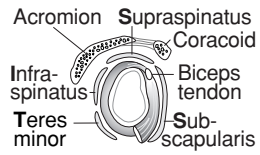
PCL = posterior cruciate ligament. LCL = lateral collateral ligament.

“Anterior” and “posterior” in ACL and PCL refer to sites of tibial attachment.

Positive anterior drawer sign indicates tearing of the ACL.

Abnormal passive abduction indicates a torn MCL.

Rotator cuff muscles



Posterior

Anterior

Shoulder muscles that form the rotator cuff:

Supraspinatus—helps deltoid abduct arm.

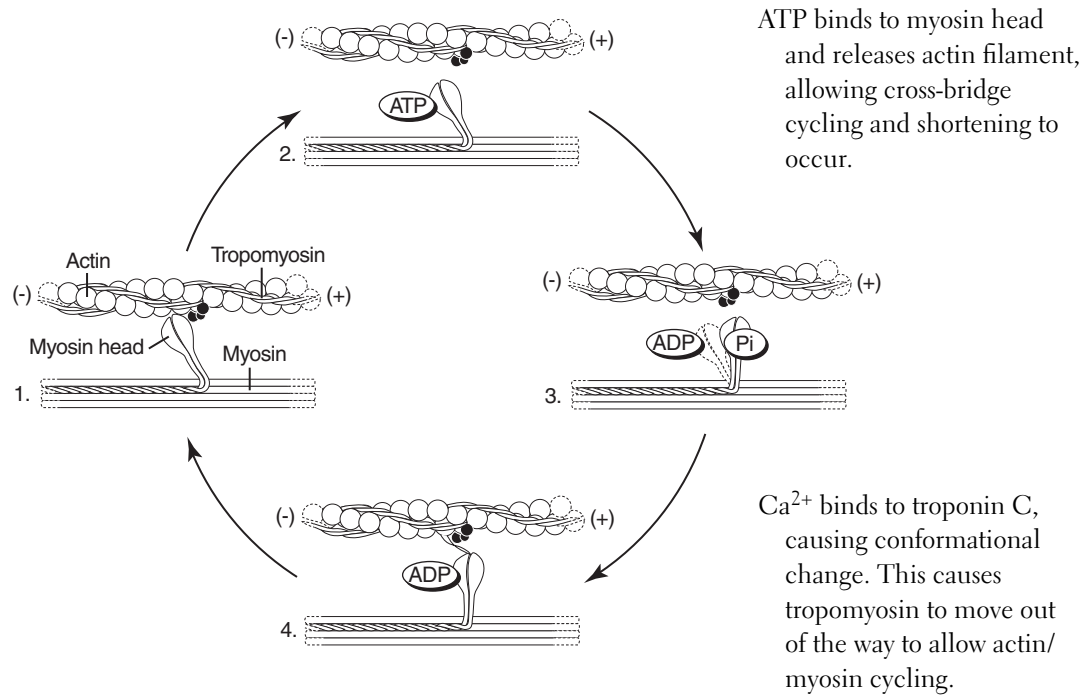
Infraspinatus—laterally rotates arm.

Teres minor—adducts and laterally rotates arm.

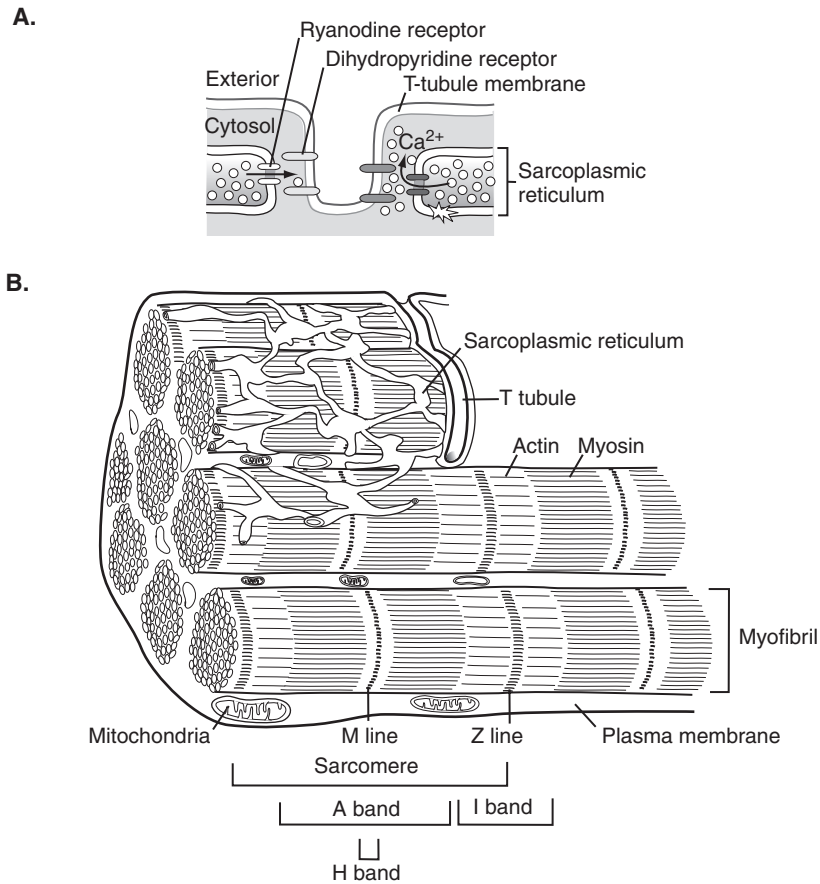
Subscapularis—medially rotates and adducts arm.

S I t S (small t is for teres minor).

Skeletal muscle contraction

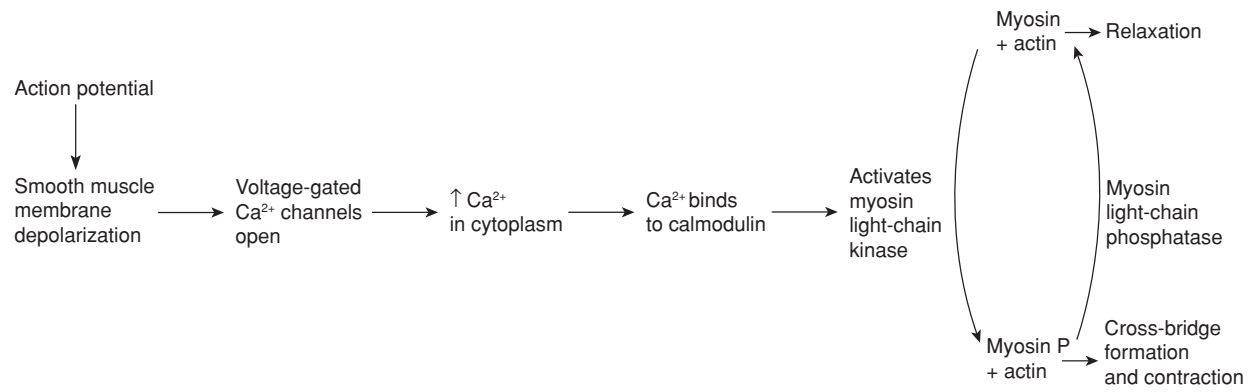


Conduction to contraction



Action potential reaches axon terminal → depolarization opens voltage-gated Ca^{2+} channels and causes neurotransmitter vesicle fusion and exocytosis. Postsynaptic ligand binding leads to depolarization of the postsynaptic (muscle) cell (**A**). Depolarization travels down T tubule. A dihydropyridine receptor (voltage-sensing Ca^{2+} channel protein) lies in the T-tubule membrane next to a ryanodine receptor, which lies in the sarcoplasmic reticulum (**B**). Released calcium binds to troponin C, which causes a conformational change and moves tropomyosin out of myosin-binding groove on actin filament. Myosin hydrolyzes its bound ATP and is displaced on the actin filament (power stroke). Contraction results in **HIZ** shrinkage—H, I, and Z bands contract (**B**). A band length stays constant throughout the cycle.

Smooth muscle contraction



Achondroplasia

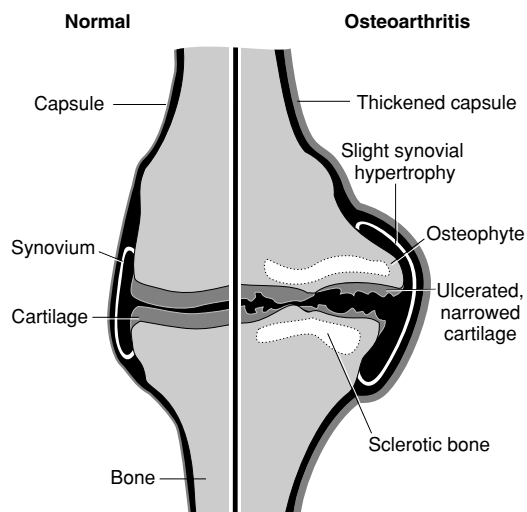
Autosomal-dominant trait. Failure of longitudinal bone growth → short limbs. Membranous ossification is not affected (skull, facial bones, and axial skeleton are normal). Head and trunk are normal in size, but limbs are much shorter than normal.

Osteoarthritis

Mechanical—wear and tear of joints leads to destruction of articular cartilage, subchondral bone formation, sclerosis, osteophytes, eburnation, Heberden's nodes (DIP), and Bouchard's nodes (PIP).

Common in older patients.

Classic presentation: pain in weight-bearing joints after use (e.g., at the end of the day), improving with rest. No systemic symptoms.



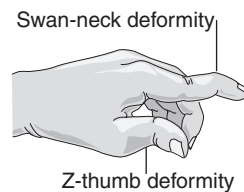
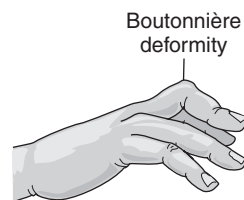
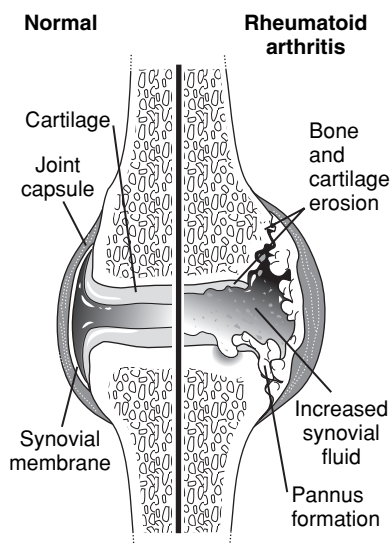
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:241.)

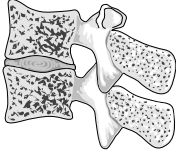
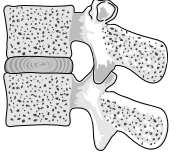
Rheumatoid arthritis

Autoimmune—inflammatory disorder affecting synovial joints, with pannus formation in joints (MCP, PIP), subcutaneous rheumatoid nodules, ulnar deviation, subluxation (see Color Image 56).

Females > males. 80% of RA patients have positive rheumatoid factor (anti-IgG antibody).

Classic presentation: morning stiffness improving with use, symmetric joint involvement, and systemic symptoms (fever, fatigue, pleuritis, pericarditis).



Osteoporosis	Reduction of bone mass in spite of normal bone mineralization.	Affects whites > blacks > Asians.
Type I	Postmenopausal; ↑ bone resorption due to ↓ estrogen levels. Estrogen replacement is controversial as prophylaxis (side effects).	Vertebral crush fractures—acute back pain, loss of height, kyphosis.
Type II	Senile osteoporosis—affects men and women > 70 years.	Distal radius (Colles') fractures, vertebral wedge fractures. Bisphosphonates or pulsatile PTH for severe cases.
<div style="display: flex; justify-content: space-around; align-items: center;">   </div> <div style="display: flex; justify-content: space-around; align-items: center;"> Mild compression fracture Normal vertebra </div>		
Osteopetrosis (marble bone disease)	Failure of normal bone resorption → thickened, dense bones. Bone defect is due to abnormal function of osteoclasts. Serum calcium, phosphate, and alkaline phosphatase are normal .	
Osteomalacia/rickets	Defective mineralization of osteoid → soft bones. Vitamin D deficiency in adults → ↓ calcium levels → ↑ secretion of PTH, ↑ in serum phosphate. Reversible when vitamin D is replaced. Vitamin D deficiency in childhood causes rickets.	
Osteitis fibrosa cystica	Caused by hyperparathyroidism. Characterized by “brown tumors” (cystic spaces lined by osteoclasts, filled with fibrous stroma and sometimes blood). High serum calcium, low serum phosphorus, and high alkaline phosphatase.	
Paget's disease (osteitis deformans)	Abnormal bone architecture caused by ↑ in both osteoblastic and osteoclastic activity. Serum calcium, phosphorus, and PTH levels are normal. Serum alkaline phosphatase is elevated .	
Polyostotic fibrous dysplasia	Bone is replaced by fibroblasts, collagen, and irregular bony trabeculae. Affects many bones. Albright's syndrome is a form of polyostotic fibrous dysplasia in which there are multiple unilateral bone lesions associated with endocrine abnormalities (precocious puberty) and unilateral pigmented skin lesions.	
Polymyalgia rheumatica	Pain and stiffness in shoulders and hips, often with fever, malaise, and weight loss. Does not cause muscular weakness. ↑ ESR. Occurs in patients > 50 years of age; associated with temporal (giant cell) arteritis. Treated with prednisone.	
Polymyositis/dermatomyositis	Polymyositis —progressive proximal muscle weakness caused by CD8 ⁺ T-cell-induced injury to myofibers. Muscle biopsy with evidence of inflammation is diagnostic. Dermatomyositis —similar to polymyositis but also involves skin rash and ↑ risk of malignancy. Labs for polymyositis/dermatomyositis show ↑ CK, ↑ aldolase, and positive ANA, anti-Jo-1.	
Mixed connective tissue disease	Raynaud's phenomenon, arthralgias, myalgias, fatigue, and esophageal hypomotility. Antibodies to U1RNP.	

Sjögren's syndrome

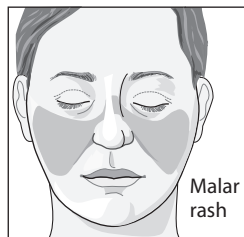
Classic triad—xerophthalmia (dry eyes, conjunctivitis), xerostomia (dry mouth, dysphagia), arthritis. Parotid enlargement, ↑ risk of B-cell lymphoma. Autoantibodies to ribonucleoprotein antigens, SS-A (Ro), SS-B (La). Predominantly affects **females** between 40 and 60 years of age.

Associated with rheumatoid arthritis.
Sicca syndrome—dry eyes, dry mouth, nasal and vaginal dryness, chronic bronchitis, reflux esophagitis.

Systemic lupus erythematosus

90% are female and between ages 14 and 45. Most common and severe in black females. Symptoms include fever, fatigue, weight loss, nonbacterial verrucous endocarditis, hilar adenopathy, and Raynaud's phenomenon. **Wire loop** lesions in kidney with immune complex deposition (with nephrotic syndrome); death from renal failure and infections. False positives on syphilis tests (RPR/VDRL) due to antiphospholipid antibodies. Lab tests detect presence of:

1. Antinuclear antibodies (ANA)—sensitive, but not specific for SLE
2. Antibodies to double-stranded DNA (anti-dsDNA)—very specific, poor prognosis
3. Anti-Smith antibodies (anti-Sm)—very specific, but not prognostic
4. Antihistone antibodies—drug-induced lupus (see Color Image 52)



Malar rash

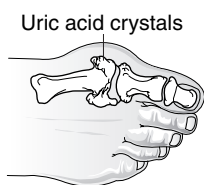
I'M DAMN SHARP:

Immunoglobulins
(anti-dsDNA, anti-Sm, antiphospholipid)
Malar rash
Discoid rash
Antinuclear antibody
Mucositis (oropharyngeal ulcers)
Neurologic disorders
Serositis (pleuritis, pericarditis)
Hematologic disorders
Arthritis
Renal disorders
Photosensitivity

Celiac sprue

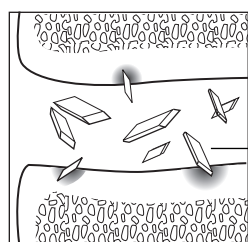
Autoimmune-mediated intolerance of gliadin (wheat) leading to steatorrhea. Associated with people of northern European descent. Findings include blunting of villi, lymphocytes in the lamina propria, and abnormal D-xylose test. Tends to affect jejunum. Associated with dermatitis herpetiformis. 10–15% lead to malignancy (most often T-cell lymphoma).

Gout



Uric acid crystals

Precipitation of monosodium urate crystals into joints due to hyperuricemia, which can be caused by Lesch-Nyhan syndrome, PRPP excess, ↓ excretion of uric acid, or glucose-6-phosphatase deficiency. Also associated with the use of thiazide diuretics, which competitively inhibit the secretion of uric acid. Asymmetric joint distribution. Classic manifestation is painful MTP joint in the big toe (podagra). Tophus formation (often on external ear or Achilles tendon). Crystals are needle shaped and **negatively birefringent**. More common in men. Acute attack tends to occur after alcohol consumption or a large meal (see Color Image 54). Treatment includes allopurinol, probenecid, colchicine, and NSAIDs.

Pseudogout

Caused by deposition of calcium pyrophosphate crystals within the joint space. Forms basophilic, rhomboid crystals that are **weakly positively birefringent** (as opposed to the negatively birefringent, needle-shaped crystals in gout). Usually affects large joints (classically the knee). > 50 years old; both sexes affected equally. No treatment.

Calcium pyrophosphate crystals

Goodpasture's syndrome

Findings: pulmonary hemorrhages → hemoptysis; renal lesions → hematuria, anemia, crescentic glomerulonephritis. Anti-glomerular basement membrane antibodies produce linear staining on immunofluorescence.

There are 2 Good Pastures for this disease: **G**lomerulus and **P**ulmonary. A type II hypersensitivity disease. Most common in men 20–40 years.

Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas and elevated serum ACE levels. Common in black females. Associated with restrictive lung disease, bilateral hilar lymphadenopathy, erythema nodosum, Bell's palsy, epithelial granulomas containing microscopic Schaumann and asteroid bodies, uveoparotitis, and hypercalcemia (due to elevated conversion of vitamin D to its active form in epithelioid macrophages) (see Image 104).

GRAIN:

Gammaglobulinemia
Rheumatoid arthritis
ACE increase
Interstitial fibrosis
Noncaseating granulomas

Seronegative spondyloarthropathies

Ankylosing spondylitis

Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (gene that codes for HLA MHC I). Occurs more often in males.

Reiter's syndrome

Chronic inflammatory disease of spine and sacroiliac joints → ankylosis (stiff spine), uveitis, and aortic regurgitation.

Classic triad:
1. Urethritis
2. Conjunctivitis and anterior uveitis
3. Arthritis

“Can't **see** (anterior uveitis/conjunctivitis), can't **pee** (urethritis), can't climb a **tree** (arthritis).”

Post-GI or chlamydia infections.

Scleroderma (progressive systemic sclerosis—PSS)

Excessive fibrosis and collagen deposition throughout the body. 75% female. Commonly sclerosis of skin but also of cardiovascular and GI systems and kidney. 2 major categories:

1. Diffuse scleroderma—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody.
2. **CREST** syndrome—**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia. Limited skin involvement, often confined to fingers and face. More benign clinical course. Associated with anticentromere antibody (see Color Image 53).

Skin disorders

Dermatitis	A group of inflammatory pruritic skin disorders. Etiology: allergy (usually type IV hypersensitivity), chemical injury, or infection.	
Atopic dermatitis (eczema)	Pruritic eruption, commonly on flexor surfaces. Often associated with other atopic diseases (asthma, allergic rhinitis).	
Allergic contact dermatitis	Type IV hypersensitivity reaction that follows exposure to allergen (poison ivy, poison oak, nickel, rubber, chemicals). Lesions occur at site of contact.	
Psoriasis	Epidermal hyperplasia (acanthosis) with parakeratotic scaling (nuclei still in stratum corneum) especially on knees and elbows. ↑ stratum spinosum, ↓ stratum granulosum (see Color Image 65). Auspitz sign.	
Dermatitis herpetiformis	Pruritic papules and vesicles. Associated with celiac disease.	
Lichen planus	Pruritic, purple, polygonal papules; infiltrate of lymphocytes at dermoepidermal junction.	
Erythema multiforme	Associated with infections, drugs, cancers, and autoimmune disease. Presents with multiple types of lesions, including macules, papules, vesicles, and target lesions (red papules with a pale central area). Stevens-Johnson syndrome is the major form of erythema multiforme. Characterized by high fever, bulla formation and necrosis, ulceration of skin, and a high mortality rate.	
Seborrheic keratosis	Flat, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts). Benign.	
Actinic keratosis	Caused by sun exposure. Small, rough erythematous or brownish papules. Premalignant lesion. Risk of carcinoma is proportional to epithelial dysplasia.	
Keloid	Tumor of connective tissue elements of dermis that causes raised, thickened scars. Follows trauma to skin, especially in African-Americans.	
Bullous pemphigoid	Autoimmune disorder with IgG antibody against epidermal basement membrane (linear immunofluorescence). Similar to but less severe than pemphigus vulgaris—affects skin but spares oral mucosa (see Color Image 64).	
Pemphigus vulgaris	Potentially fatal autoimmune skin disorder. Intra-dermal bullae involving the oral mucosa and skin. Findings: acantholysis (breakdown of epithelial cell-to-cell junctions), IgG antibody against epidermal cell surface (immunofluorescence throughout epidermis) (see Color Image 63).	

Skin cancer

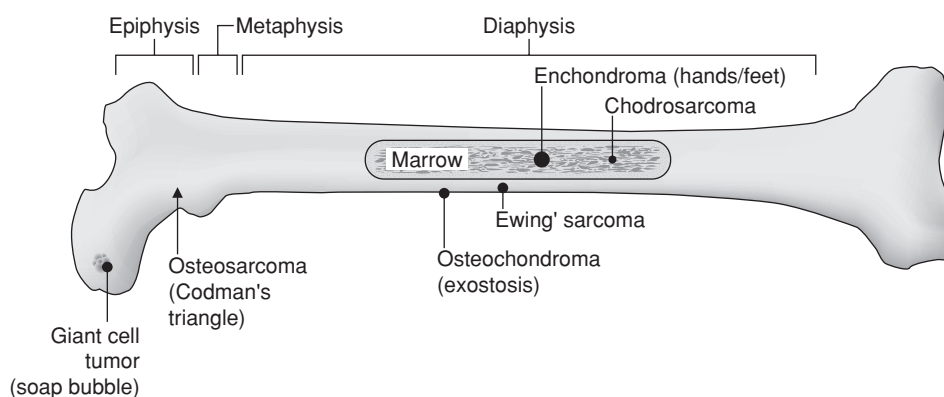
Squamous cell carcinoma	Very common. Associated with excessive exposure to sunlight and arsenic exposure. Commonly appear on hands and face. Locally invasive, but rarely metastasizes. Histopathology: keratin “pearls” (see Color Image 60).	Actinic keratosis is a precursor to squamous cell carcinoma.
Basal cell carcinoma	Most common in sun-exposed areas of body. Locally invasive, but almost never metastasizes. Gross pathology: pearly papules (see Color Image 62).	Basal cell tumors have “palisading” nuclei.
Melanoma	Common tumor with significant risk of metastasis. Associated with sunlight exposure; fair-skinned persons are at ↑ risk. Incidence ↑. Depth of tumor correlates with risk of metastasis (see Color Image 61).	Dysplastic nevus is a precursor to melanoma.

Primary bone tumors**Benign**

- Giant cell tumor** Occurs most commonly at epiphyseal end of long bones. Peak incidence 20–40 years old. Locally aggressive benign tumor often around the distal femur, proximal tibial region. Characteristic “double bubble” or “soap bubble” appearance on x-ray. Spindle-shaped cells with multinucleated giant cells.
- Osteochondroma (exostosis)** Most common benign bone tumor. Usually in men < 25 years of age. Commonly originates from long metaphysis. Malignant transformation to chondrosarcoma is rare.
- Enchondroma** Benign cartilaginous neoplasm found in intramedullary bone. Usually distal extremities (vs. chondrosarcoma).

Malignant

- Osteosarcoma (osteogenic carcinoma)** Most common 1° malignant tumor of bone. Peak incidence in men 10–20 years old. Commonly found in the metaphysis of long bones. Predisposing factors include Paget’s disease of bone, bone infarcts, radiation, and familial retinoblastoma. Codman’s triangle (from elevation of periosteum) on x-ray.
- Ewing’s sarcoma** Anaplastic small blue cell malignant tumor. Most common in boys < 15. Extremely aggressive with early mets, but responsive to chemotherapy. Characteristic “onion-skin” appearance in bone (“going out for Ewings and onion rings.”) Commonly appears in diaphysis of long bones, pelvis, scapula, and ribs. 11;22 translocation.
- Chondrosarcoma** Malignant cartilaginous tumor. Most common in men aged 30–60. Usually located in pelvis, spine, scapula, humerus, tibia, or femur. May be of 1° origin or from osteochondroma.

**Buerger’s disease**

Also known as thromboangiitis obliterans; idiopathic, segmental, thrombosing vasculitis of intermediate and small peripheral arteries and veins. Seen in heavy smokers.

Findings

Intermittent claudication, superficial nodular phlebitis, cold sensitivity (Raynaud’s phenomenon), severe pain in affected part; may lead to gangrene.

Treatment

Quit smoking.

Takayasu’s arteritis

Known as “pulseless disease”—granulomatous thickening of aortic arch and/or proximal great vessels. Associated with an elevated ESR. Primarily affects Asian females < 40 years old. **F**ever, **A**rthritis, **N**ight sweats, **M**yalgia, **S**KIN nodules, **O**cular disturbances, **W**eak pulses in upper extremities.

Affects medium and large arteries.

FAN MY SKIN On
Wednesday.

**Temporal arteritis
(giant cell
arteritis)**

Most common vasculitis that affects medium and small arteries, usually branches of carotid artery. Focal, granulomatous. Findings include unilateral headache, jaw claudication, impaired vision (occlusion of ophthalmic artery, which can lead to blindness). Half of patients have systemic involvement and polymyalgia rheumatica (proximal muscle pain, periarticular pain). Associated with elevated ESR. Responds well to steroids.

TEMporal = signs near **TEM**ples. ESR is markedly elevated. Affects elderly females.

**Polyarteritis
nodosa**

Symptoms

Findings

Treatment

Characterized by necrotizing immune complex inflammation of medium-sized muscular arteries, typically involving renal and visceral vessels.
Fever, weight loss, malaise, abdominal pain, melena, headache, myalgia, hypertension, neurologic dysfunction, cutaneous eruptions.
Hepatitis B seropositivity in 30% of patients. Multiple aneurysms and constrictions on arteriogram. Not associated with ANCA.
Corticosteroids, cyclophosphamide.

Lesions are of different ages.

**Wegener's
granulomatosis**

Symptoms

Findings

Treatment

Characterized by triad of focal necrotizing vasculitis, necrotizing granulomas in the lung and upper airway, and necrotizing glomerulonephritis.
Perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis, cough, dyspnea, hemoptysis, hematuria.
C-ANCA is a strong marker of disease; chest x-ray may reveal large nodular densities; hematuria and red cell casts.
Cyclophosphamide and corticosteroids.

Other ANCA-positive vasculitides

Microscopic
polyangiitis

1° pauci-immune
crescentic
glomerulo-
nephritis

Churg-Strauss
syndrome

Like Wegener's but lacks granulomas. P- or C-ANCA.

Vasculitis limited to kidney.

Granulomatous vasculitis with eosinophilia. Involves lung, heart, skin, kidneys, nerves. Often seen in atopic patients.

Kawasaki disease

Acute, self-limiting disease of infants/kids. Acute necrotizing vasculitis of small/medium-sized vessels. Fever, congested conjunctiva, changes in lips/oral mucosa, lymphadenitis. May develop coronary aneurysms.

**Henoch-Schönlein
purpura**

Most common form of childhood systemic vasculitis. Skin rash, arthralgia, intestinal hemorrhage, abdominal pain, and melena.

Opioid analgesics	Morphine, fentanyl, codeine, heroin, methadone, meperidine, dextromethorphan.
Mechanism	Act as agonists at opioid receptors (μ = morphine, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission.
Clinical use	Pain, cough suppression (dextromethorphan), diarrhea (loperamide and diphenoxylate), acute pulmonary edema, maintenance programs for addicts (methadone).
Toxicity	Addiction, respiratory depression , constipation, miosis (pinpoint pupils), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltrexone (opioid receptor antagonist). O_2 is contraindicated if morphine overdose—might contribute to respiratory failure.

NSAIDs	Ibuprofen, naproxen, indomethacin, ketorolac.
Mechanism	Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.
Clinical use	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.
Toxicity	Renal damage, aplastic anemia, GI distress, ulcers.

COX-2 inhibitors (celecoxib, valdecoxib)

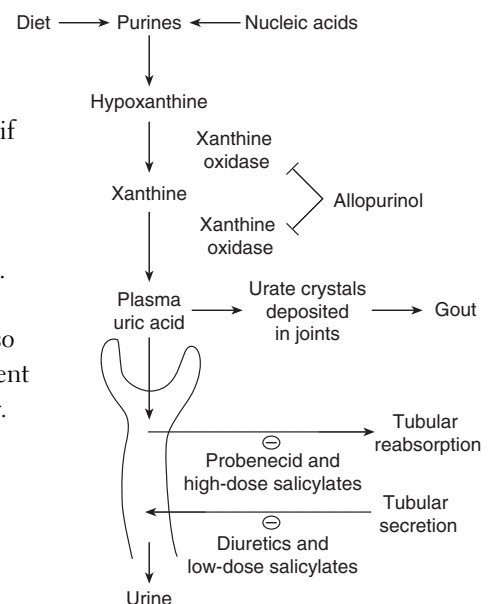
Mechanism	Selectively inhibit cyclooxygenase (COX) isoform 2, which is found in inflammatory cells and mediates inflammation and pain; spares COX-1, which helps maintain the gastric mucosa. Thus, should not have the corrosive effects of other NSAIDs on the GI lining.
Clinical use	Rheumatoid and osteoarthritis.
Toxicity	Similar to other NSAIDs; may have less toxicity to GI mucosa (i.e., lower incidence of ulcers, bleeding).

Acetaminophen

Mechanism	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
Clinical use	Antipyretic, analgesic, but lacking anti-inflammatory properties.
Toxicity	Overdose produces hepatic necrosis; acetaminophen metabolite depletes glutathione and forms toxic tissue adducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

Gout drugs

Colchicine	Acute gout. Depolymerizes microtubules, impairing leukocyte chemotaxis and degranulation. GI side effects, especially if given orally. (Note: indomethacin is less toxic, more commonly used.)
Probenecid	Chronic gout. Inhibits reabsorption of uric acid (also inhibits secretion of penicillin).
Allopurinol	Chronic gout. Inhibits xanthine oxidase, ↓ conversion of xanthine to uric acid. Also used in lymphoma and leukemia to prevent tumor lysis—associated urate nephropathy.



Etanercept

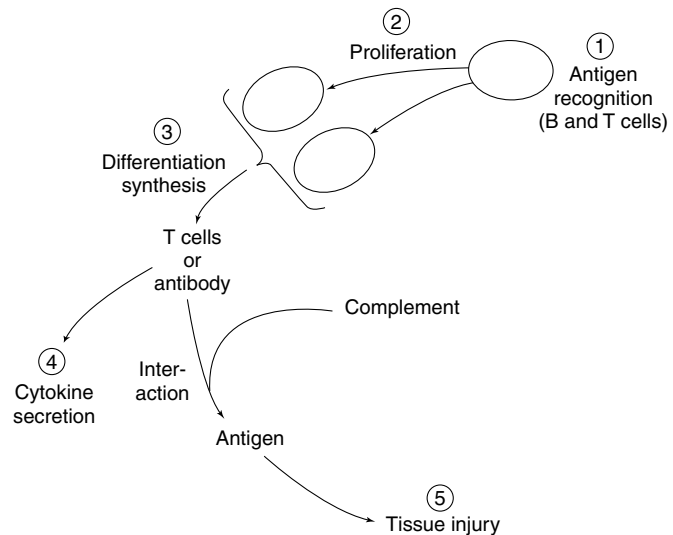
Mechanism	Recombinant form of human TNF receptor that binds TNF- α .
Clinical use	Rheumatoid arthritis, psoriasis, ankylosing spondylitis.

Infliximab

Mechanism	TNF- α antibody.
Clinical use	Crohn's disease, rheumatoid arthritis, ankylosing spondylitis.

Immunosuppressive agents: sites of action

Agent	Site
Prednisone	2, 5
Cyclosporine	2, 3
Azathioprine	2
Methotrexate	2
Dactinomycin	2, 3
Cyclophosphamide	2
Antilymphocytic globulin and monoclonal anti-T-cell antibodies	1, 2, 3
Rh ₃ (D) immune globulin	1
Tacrolimus	4



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:924.)

Cyclosporine

Mechanism	Binds to cyclophilins. Complex blocks the differentiation and activation of T cells by inhibiting calcineurin, thus preventing the production of IL-2 and its receptor.
Clinical use	Suppresses organ rejection after transplantation; selected autoimmune disorders.
Toxicity	Predisposes patients to viral infections and lymphoma; nephrotoxic (preventable with mannitol diuresis).

Tacrolimus (FK506)

Mechanism	Similar to cyclosporine; binds to FK-binding protein, inhibiting secretion of IL-2 and other cytokines.
Clinical use	Potent immunosuppressive used in organ transplant recipients.
Toxicity	Significant—nephrotoxicity, peripheral neuropathy, hypertension, pleural effusion, hyperglycemia.

Azathioprine

Mechanism	Antimetabolite derivative of 6-mercaptopurine that interferes with the metabolism and synthesis of nucleic acids. Toxic to proliferating lymphocytes.
Clinical use	Kidney transplantation, autoimmune disorders (including glomerulonephritis and hemolytic anemia).
Toxicity	Bone marrow suppression. Active metabolite mercaptopurine is metabolized by xanthine oxidase; thus, toxic effects may be ↑ by allopurinol.

Recombinant cytokines and clinical uses

Agent	Clinical uses
Aldesleukin (interleukin-2)	Renal cell carcinoma, metastatic melanoma
Erythropoietin (epoetin)	Anemias (especially in renal failure)
Filgrastim (granulocyte colony-stimulating factor)	Recovery of bone marrow
Sargramostim (granulocyte-macrophage colony-stimulating factor)	Recovery of bone marrow
α -interferon	Hepatitis B and C, Kaposi's sarcoma, leukemias, malignant melanoma
β -interferon	Multiple sclerosis
γ -interferon	Chronic granulomatous disease
Oprelvekin (interleukin-11)	Thrombocytopenia
Thrombopoietin	Thrombocytopenia

NOTES

[illegible]

Neurology and Psychiatry

*“What a terrible thing to have lost one’s mind. Or not to have a mind at all.
How true that is.”*

—Dan Quayle

“He has two neurons held together by a spirochete.”

—Anonymous

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy and Physiology
- ▶ Pathology
- ▶ Pharmacology

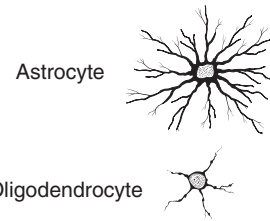
■ Patient presents with ↓ pain and temperature sensation over the lateral aspects of both arms.	What is the lesion?	Syringomyelia.
■ Penlight in patient's right eye produces bilateral pupillary constriction. When moved to the left eye, there is paradoxical dilatation.	What is the defect?	Atrophy of the left optic nerve.
■ Patient describes ↓ prick sensation on the lateral aspect of her leg and foot.	A deficit in what muscular action can also be expected?	Dorsiflexion and eversion of foot (common peroneal nerve).
■ Elderly woman presents with arthritis and tingling over the lateral digits of her right hand.	What is the diagnosis?	Carpal tunnel syndrome, median nerve compression.
■ 20-year-old dancer reports ↓ plantar flexion and ↓ sensation over the back of her thigh, calf, and lateral half of her foot.	What spinal nerve is involved?	Tibial (L4–S3).
■ Woman involved in a motor vehicle accident cannot turn her head to the left and has right shoulder droop.	What structure is damaged?	Right CN XI (runs through jugular foramen with CN IX and X), innervating sternocleidomastoid and trapezius muscles.
■ Man presents with one wild, flailing arm.	Where is the lesion?	Contralateral subthalamic nucleus (hemiballismus).
■ Patient with cortical lesion does not know that he has a disease.	Where is the lesion?	Right parietal lobe.
■ Patient cannot protrude tongue toward left side and has a right-sided spastic paralysis.	Where is the lesion?	Left medulla, CN XII.
■ Teen falls while rollerblading and hurts his elbow. He can't feel the medial part of his palm.	Which nerve and what injury?	Ulnar nerve due to broken medial condyle.
■ Field hockey player presents to the ER after falling on her arm during practice. X-ray shows midshaft break of the humerus.	Which nerve and which artery are most likely damaged?	Radial nerve and deep brachial artery, which run together.
■ Patient cannot blink his right eye or seal his lips and has mild ptosis on the right side.	What is the diagnosis, and which nerve is affected?	Bell's palsy; CN VII.
■ Patient complains of pain, numbness, and a tingling sensation. On exam, she has wasting of the thenar eminence.	What is the diagnosis, and what nerve is often affected?	Carpal tunnel syndrome; median nerve.

► **NEUROLOGY AND PSYCHIATRY—HIGH-YIELD CLINICAL VIGNETTES** (*continued*)

■ During a particular stage of sleep, man has variable blood pressure, penile tumescence, and variable EEG.	What stage of sleep is he in?	REM sleep.
■ Person demands only the best and most famous doctor in town.	What is the personality disorder?	Narcissistic personality disorder.
■ Nurse has episodes of hypoglycemia; blood analysis reveals no elevation in C protein.	What is the diagnosis?	Factitious disorder; self-scripted insulin.
■ 55-year-old businessman complains of lack of successful sexual contacts with women and lack of ability to reach a full erection. Two years ago he had a heart attack.	What might be the cause of his problem?	Fear of sudden death during intercourse.
■ 15-year-old girl of normal height and weight for her age has enlarged parotid glands but no other complaints. The mother confides that she found laxatives in the daughter's closet.	What is the diagnosis?	Bulimia.
■ Woman presents with headache, visual disturbance, galactorrhea, and amenorrhea.	What is the diagnosis?	Prolactinoma.
■ 43-year-old man experiences dizziness and tinnitus. CT shows enlarged internal acoustic meatus.	What is the diagnosis?	Schwannoma.
■ 25-year-old female presents with sudden unioocular vision loss and slightly slurred speech. She has a history of weakness and paresthesias that have resolved.	What is the diagnosis?	Multiple sclerosis.
■ 10-year-old child "spaces out" in class (e.g., stops talking midsentence and then continues as if nothing had happened). During spells, there is slight quivering of lips.	What is the diagnosis?	Absence seizures.
■ Man on several medications, including antidepressants and antihypertensives, has mydriasis and becomes constipated.	What is the cause of his symptoms?	TCA.
■ Woman on MAO inhibitor has hypertensive crisis after a meal.	What did she ingest?	Tyramine (wine or cheese).

**CNS/PNS
supportive cells**

Astrocytes—physical support, repair, K^+ metabolism; help maintain blood-brain barrier. Astrocyte marker: GFAP.
Ependymal cells—inner lining of ventricles.
Microglia—phagocytosis.
Oligodendroglia—central myelin production.
Schwann cells—peripheral myelin production.
Microglia, like macrophages, originate from mesoderm. All other CNS/PNS supportive cells originate from ectoderm.



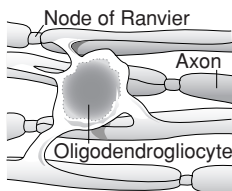
Microglia



CNS phagocytes. Mesodermal origin. Not readily discernible in Nissl stains. Have small irregular nuclei and relatively little cytoplasm. In response to tissue damage, transform into large ameboid phagocytic cells.

HIV-infected microglia fuse to form multinucleated giant cells in the CNS.

Oligodendroglia



Each oligodendrocyte myelinates multiple CNS axons, up to 30 each. In Nissl stains, they appear as small nuclei with dark chromatin and little cytoplasm. Predominant type of glial cell in white matter.

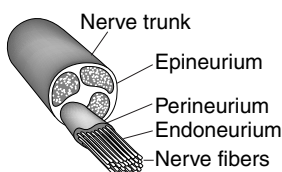
These cells are destroyed in multiple sclerosis.

Schwann cells

Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration.

Acoustic neuroma is an example of a schwannoma. Location commonly associated with internal acoustic meatus (CN VII, VIII).

**Peripheral nerve
layers**



Endoneurium invests single nerve fiber.
Perineurium (permeability barrier) surrounds a fascicle of nerve fibers.
Epineurium (dense connective tissue) surrounds entire nerve (fascicles and blood vessels).

Perineurium—Permeability barrier; must be rejoined in microsurgery for limb reattachment.
Endo = inner.
Peri = around.
Epi = outer.

Sensory corpuscles

Meissner's

Small, encapsulated nerve endings found in dermis of palms, soles, and digits of skin. Involved in light discriminatory touch of glabrous (hairless) skin.



Pacinian

Large, encapsulated nerve endings found in deeper layers of skin at ligaments, joint capsules, serous membranes, mesenteries. Involved in pressure, coarse touch, vibration, and tension.

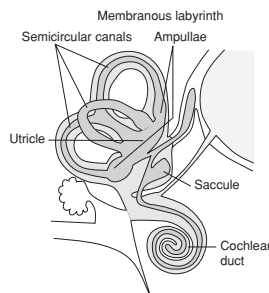


Merkel's

Cup-shaped nerve endings (tactile disks) in dermis of fingertips, hair follicles, hard palate. Involved in light, crude touch.



Inner ear



Consists of a series of tubes in the temporal bone (bony labyrinth) filled with perilymph (Na^+ rich, similar to ECF) that includes cochlea, vestibule, and semicircular canals. Within the bony labyrinth is a 2nd series of tubes (membranous labyrinth) filled with endolymph (K^+ rich, similar to ICF) that includes cochlear duct (within the cochlea), utricle and saccule (within the vestibule), and semicircular canals. Hair cells are the sensory elements in both vestibular apparatus (spatial orientation) and cochlea (hearing).

Base of the cochlea (narrow and stiff) picks up high-frequency sound. Apex of the cochlea (wide and flexible) picks up low-frequency sound.

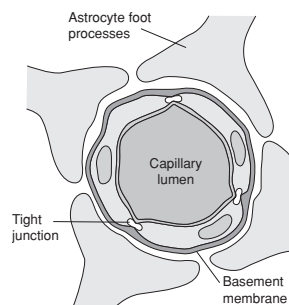
Peri—think outside of cell (Na^+).
Endo—think inside of cell (K^+).
Endolymph is made by the stria vascularis.

Utricle and saccule contain maculae—detect linear acceleration.

Semicircular canals contain Ampullae—detect Angular acceleration.

Hearing loss in the elderly—high frequency \rightarrow low frequency.

Blood-brain barrier



Formed by 3 structures:

1. Tight junctions between nonfenestrated capillary endothelial cells
2. Astrocyte processes
3. Basement membrane

Glucose and amino acids cross by carrier-mediated transport mechanism.

Nonpolar/lipid-soluble substances cross more readily than do polar/water-soluble ones.

A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in the blood to affect brain function (e.g., area postrema—vomiting after chemo) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release).

Other barriers include:

1. Blood-testis barrier
2. Maternal-fetal blood barrier of placenta

Hypothalamus functions

Thirst and water balance (supraoptic nucleus).
 Adenohypophysis control via releasing factors.
 Neurohypophysis releases hormones synthesized in hypothalamic nuclei.
Hunger (lateral nucleus—destruction → anorexia and starvation) and satiety (ventromedial nucleus—destruction → hyperphagia and obesity).
 Autonomic regulation (anterior hypothalamus regulates parasympathetic; posterior hypothalamus regulates sympathetic), circadian rhythms (suprachiasmatic nucleus).
 Temperature regulation (posterior hypothalamus regulates heat conservation and production when cold; Anterior hypothalamus coordinates Cooling when hot).
 Sexual urges and emotions (Septal nucleus—destruction → rage).

The hypothalamus wears **TAN HATS**.

If you zap your **ventromedial** nucleus, you grow **ventrally** and **medially**.

If you zap your **Posterior** hypothalamus, you become a **Poikilotherm** (cold-blooded snake).

A/C = anterior cooling.

Posterior pituitary (neurohypophysis)

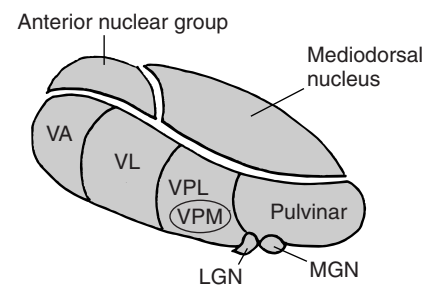
Receives hypothalamic axonal projections from supraoptic (ADH) and paraventricular (oxytocin) nuclei.

Oxytocin: *oxys* = quick; *tocos* = birth.

Thalamus

Major relay for ascending sensory information that ultimately reaches the cortex.
Lateral geniculate nucleus (LGN)—visual.
Medial geniculate nucleus (MGN)—auditory.
Ventral posterior nucleus, lateral part (VPL)—body sensation (proprioception, pressure, pain, touch, vibration via dorsal columns, spinothalamic tract).
Ventral posterior nucleus, medial part (VPM)—facial sensation (via CN V).
Ventral anterior/lateral (VA/VL) nuclei—motor.

Lateral for Light.
Medial for Music.



Limbic system

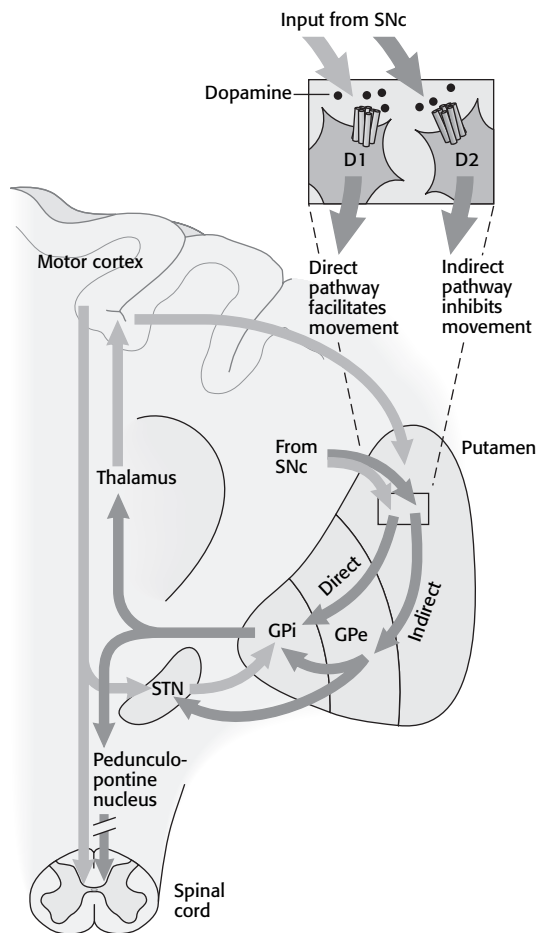
Responsible for Feeding, Fighting, Feeling, Flight, and sex.

The famous 5 F's.

Basal ganglia

Important in voluntary movements and making postural adjustments.

Parkinson's disease symptoms due to ↓ input from the substantia nigra (leading to ↓ stimulation of the direct pathway and ↓ inhibition of the indirect pathway).



■ stimulatory

■ inhibitory

SNc Substantia nigra pars compacta

GPe Globus pallidus externus

GPi Globus pallidus internus

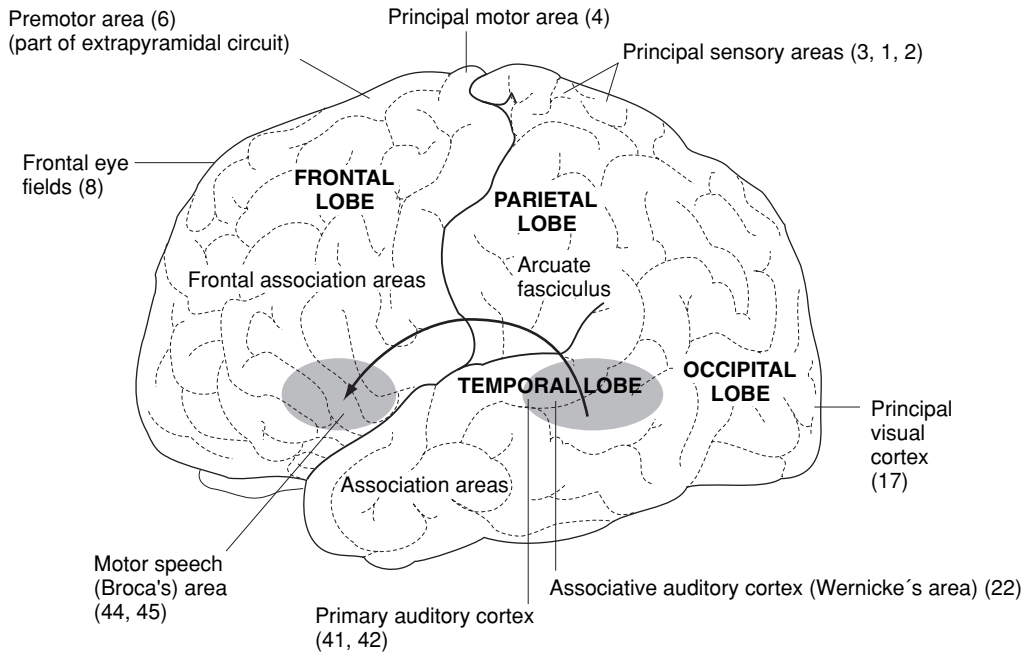
STN Subthalamic nucleus

D1 Dopamine D1 receptor

D2 Dopamine D2 receptor

(Adapted, with permission, from Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*, 4th ed. Stamford, CT: Appleton & Lange, 2000.)

Cerebral cortex functions

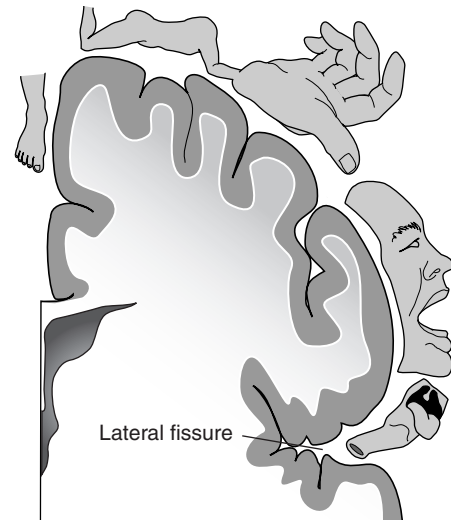


Frontal lobe functions

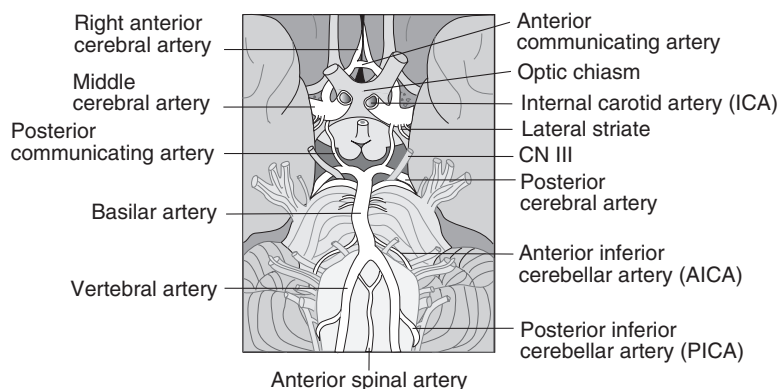
“Executive functions”—planning, inhibition, concentration, orientation, language, abstraction, judgment, motor regulation, mood. Lack of social judgment is most notable in frontal lobe lesion.

Homunculus

Topographical representation of sensory and motor areas in the cerebral cortex. Use to localize lesion (e.g., in blood supply) leading to specific defects. For example, lower extremity deficit in sensation or movement indicates involvement of the anterior cerebral artery (see following entry).



Circle of Willis



Anterior cerebral artery—supplies medial surface of the brain, leg-foot area of motor and sensory cortices.

Middle cerebral artery—supplies lateral aspect of brain, trunk-arm-face area of motor and sensory cortices, Broca's and Wernicke's speech areas.

Anterior communicating artery—most common circle of Willis aneurysm; may cause visual-field defects.

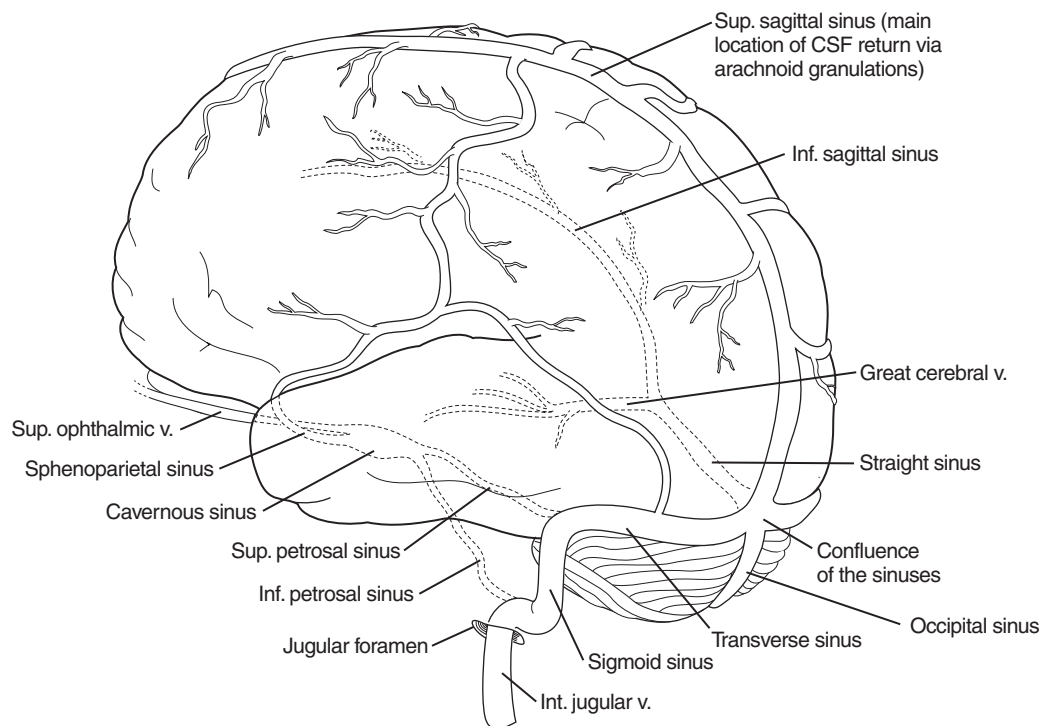
Posterior communicating artery—common area of aneurysm; causes CN III palsy.

Lateral striate—divisions of middle cerebral artery; “arteries of stroke”; supply internal capsule, caudate, putamen, globus pallidus.

In general, stroke of anterior circle → general sensory and motor dysfunction, aphasia; stroke of posterior circle → cranial nerve deficits (vertigo, visual deficits), coma, cerebellar deficits (ataxia).

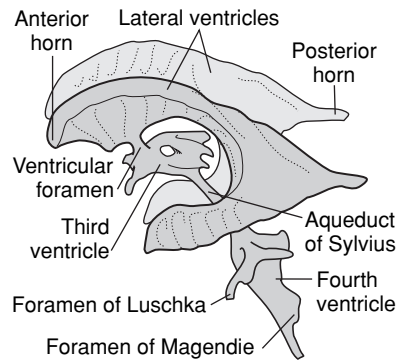
Dural venous sinuses

Venous sinuses run in the dura mater where its meningeal and periosteal layers separate. Cerebral veins → venous sinuses → internal jugular vein.



(Adapted, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003.)

Ventricular system



Lateral ventricle → 3rd ventricle via foramen of Monro.
 3rd ventricle → 4th ventricle via aqueduct of Sylvius.
 4th ventricle → subarachnoid space via:
 Foramina of Luschka = lateral.
 Foramen of Magendie = medial.

Spinal nerves

There are 31 spinal nerves altogether: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.

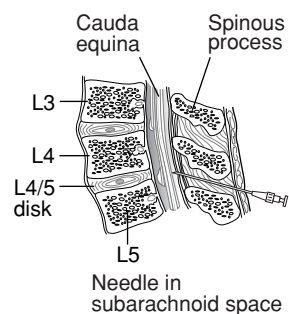
31, just like 31 flavors!
 Vertebral disk herniation usually occurs between L5 and S1.

Spinal cord lower extent

In adults, spinal cord extends to lower border of L1–L2; subarachnoid space extends to lower border of S2. Lumbar puncture is usually performed in L3–L4 or L4–L5 interspaces, at level of cauda equina.

To keep the cord **alive**, keep the spinal needle between **L3 and L5**.

Lumbar puncture



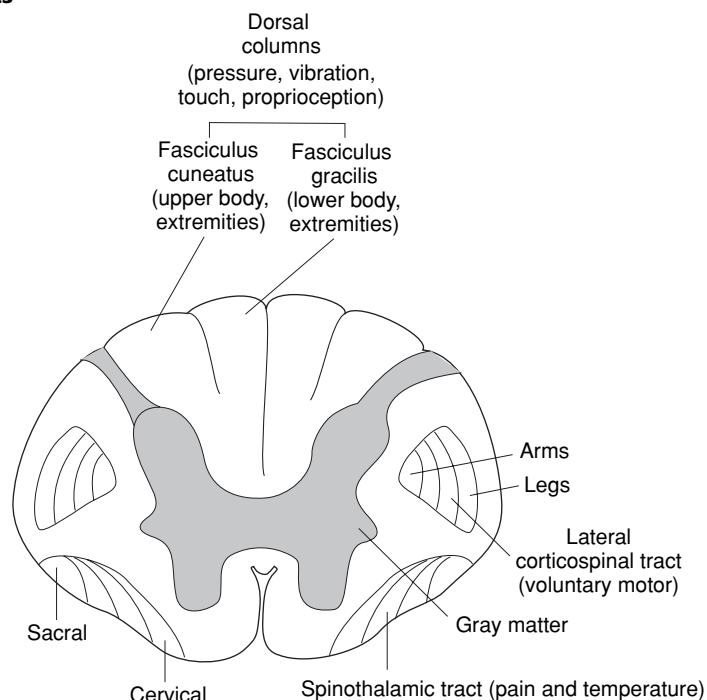
CSF obtained from lumbar subarachnoid space between L4 and L5 (at the level of iliac crests).

Structures pierced as follows:

1. Skin/superficial fascia
2. Ligaments (supraspinous, interspinous, ligamentum flavum)
3. Epidural space
4. Dura mater
5. Subdural space
6. Arachnoid
7. Subarachnoid space—CSF

Pia is not pierced.

Spinal cord and associated tracts



Spinal tract anatomy and functions

Tract and function	1st-order neuron	Synapse 1	2nd-order neuron	Synapse 2	3rd-order neuron
Dorsal column-medial lemniscal pathway (ascending pressure, vibration, touch, and proprioceptive sensation)	Sensory nerve ending → dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column	Nucleus cuneatus or gracilis (medulla)	Decussates in medulla → ascends contralaterally in medial lemniscus	VPL of thalamus	Sensory cortex
Spinothalamic tract (ascending pain and temperature sensation)	Sensory nerve ending (A-delta and C fibers) → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates at anterior white commissure → ascends contralaterally	VPL of thalamus	Sensory cortex
Lateral corticospinal tract (descending voluntary movement of contralateral limbs)	Upper motor neuron: 1° motor cortex → descends ipsilaterally until decussating at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	Lower motor neuron: Leaves spinal cord	Neuromuscular junction	

Dorsal column organization

Fasciculus gracilis = legs.
Fasciculus cuneatus = arms.

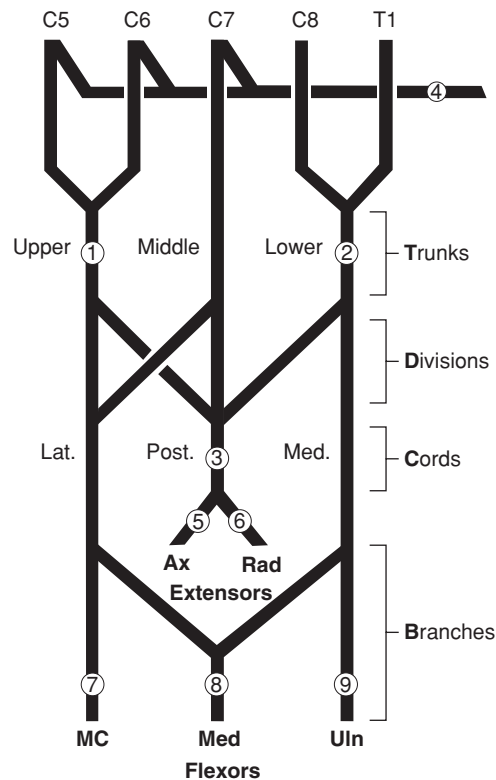
Dorsal column is organized as you are, with hands at sides—arms outside and legs inside.

Brachial plexus

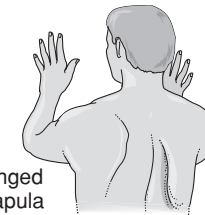
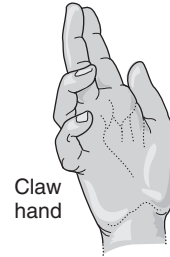
1. Waiter's tip
2. Claw hand
3. Wrist drop
4. Winged scapula
5. Deltoid paralysis
6. Saturday night palsy (wrist drop)
7. Difficulty flexing elbow, variable sensory loss
8. Decreased thumb function, Pope's blessing
9. Intrinsic muscles of hand, claw hand

Rad = radial nerve
Ax = axillary nerve
LT = long thoracic nerve
MC = musculocutaneous nerve
Med = median nerve
Uln = ulnar nerve

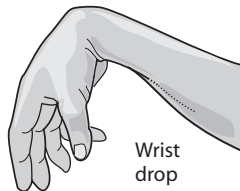
Clavicle fracture is relatively common—brachial plexus is protected from injury by subclavius muscle.



**Randy
Travis
Drinks
Cold
Beer.**



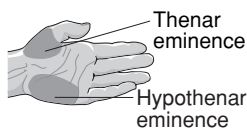
Radial nerve



Known as the “great extensor nerve.” Provides innervation of the **Brachioradialis**, **Extensors** of the wrist and fingers, **Supinator**, and **Triceps**.

Radial nerve innervates the **BEST!**
 To **SUP**inate is to move as if carrying a bowl of **SOUP**.

Thenar-hypothenar muscles

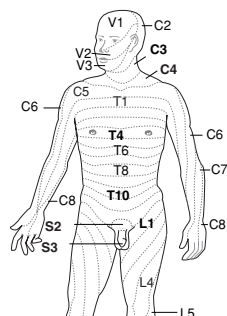


Thenar—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis.
Hypothenar—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi.

Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

Clinically important landmarks

Pudendal nerve block—ischial spine.
Appendix— $\frac{2}{3}$ of the way from the umbilicus to the anterior superior iliac spine (McBurney's point).
Lumbar puncture—iliac crest.

Landmark dermatomes

C2 is the posterior half of a skull “cap.”
 C3 is a high turtleneck shirt.
 C4 is a low-collar shirt.
 T4 is at the nipple.
 T7 is at the xiphoid process.
 T10 is at the umbilicus (important for early appendicitis pain referral).
 L1 is at the inguinal ligament.
 L4 includes the kneecaps.
 S2, S3, S4 erection and sensation of penile and anal zones.

Gallbladder pain referred to the right shoulder via the phrenic nerve.
T4 at the teat pore.

T10 at the belly butTEN.

L1 is **IL** (Inguinal Ligament).
 Down on **L4s (all fours)**.
 “S2, 3, 4 keep the penis off the floor.”

Spindle muscle control

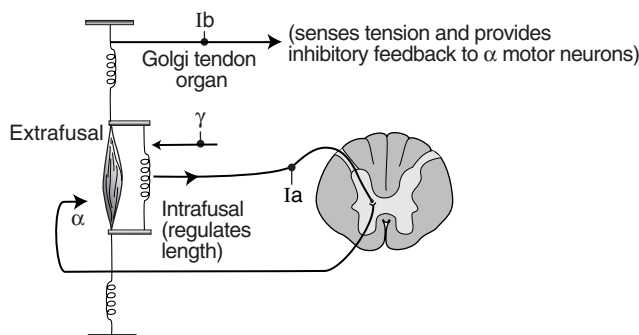
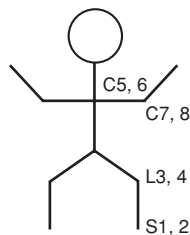
Muscle spindle

In parallel with muscle fibers. Muscle stretch → intrafusal stretch → stimulates Ia afferent → stimulates α motor neuron → reflex muscle (extrafusal) contraction.

Gamma loop

CNS stimulates γ motor neuron → contracts intrafusal fiber → increased sensitivity of reflex arc.

Muscle spindles monitor muscle length (help you pick up a heavy suitcase when you didn’t know how heavy it was). Golgi tendon organs monitor muscle tension (make you drop a heavy suitcase you’ve been holding too long).

**Clinical reflexes**

Biceps = C5 nerve root.
 Triceps = C7 nerve root.
 Patella = L4 nerve root.
 Achilles = S1 nerve root.
 Babinski—dorsiflexion of the big toe and fanning of other toes; sign of UMN lesion, but normal reflex in 1st year of life.

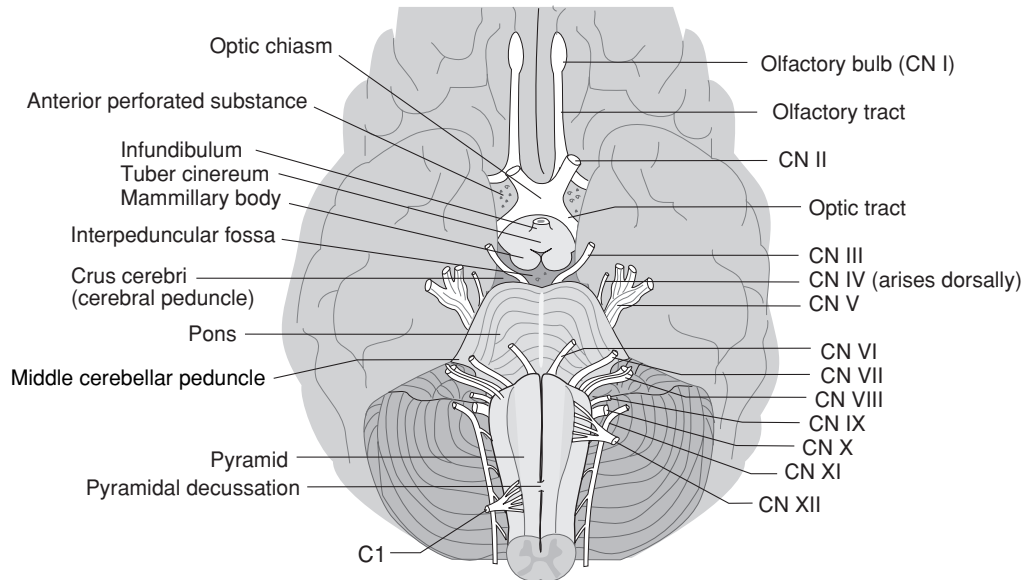
Reflexes count up in order.
 S1, 2
 L3, 4
 C5, 6
 C7, 8

Primitive reflexes

1. Moro reflex—extension of limbs when startled
2. Rooting reflex—nipple seeking
3. Palmar reflex—grasps objects in palm
4. Babinski reflex—large toe dorsiflexes with plantar stimulation

Normally disappear within 1st year. May reemerge following frontal lobe lesion.

Brain stem anatomy



CNs that lie medially at brain stem: III, VI, XII. $3(\times 2) = 6(\times 2) = 12$.

Cranial nerves

Nerve	CN	Function	Type	Mnemonic
Olfactory	I	Smell	Sensory	Some
Optic	II	Sight	Sensory	Say
Oculomotor	III	Eye movement, pupil constriction, accommodation, eyelid opening	Motor	Marry
Trochlear	IV	Eye movement	Motor	Money
Trigeminal	V	Mastication, facial sensation	Both	But
Abducens	VI	Eye movement	Motor	My
Facial	VII	Facial movement, taste from anterior $\frac{2}{3}$ of tongue, lacrimation, salivation (submaxillary and sublingual glands), eyelid closing	Both	Brother
Vestibulocochlear	VIII	Hearing, balance	Sensory	Says
Glossopharyngeal	IX	Taste from posterior $\frac{1}{3}$ of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors	Both	Big
Vagus	X	Taste from epiglottic region, swallowing, palate elevation, talking, thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	Both	Brains
Accessory	XI	Head turning, shoulder shrugging	Motor	Matter
Hypoglossal	XII	Tongue movement	Motor	Most

Cranial nerve nuclei

Located in tegmentum portion of brain stem (between dorsal and ventral portions).

Lateral nuclei = sensory.
Medial nuclei = Motor.

1. Midbrain—nuclei of CN III, IV.
2. Pons—nuclei of CN V, VI, VII, VIII.
3. Medulla—nuclei of CN IX, X, XI, XII.

Vagal nuclei

Nucleus Solitarius	Visceral Sensory information (e.g., taste, baroreceptors, gut distention).	VII, IX, X.
Nucleus ambiguus	Motor innervation of pharynx, larynx, and upper esophagus (e.g., swallowing, palate elevation).	IX, X, XI.
Dorsal motor nucleus	Sends autonomic (parasympathetic) fibers to heart, lungs, and upper GI.	

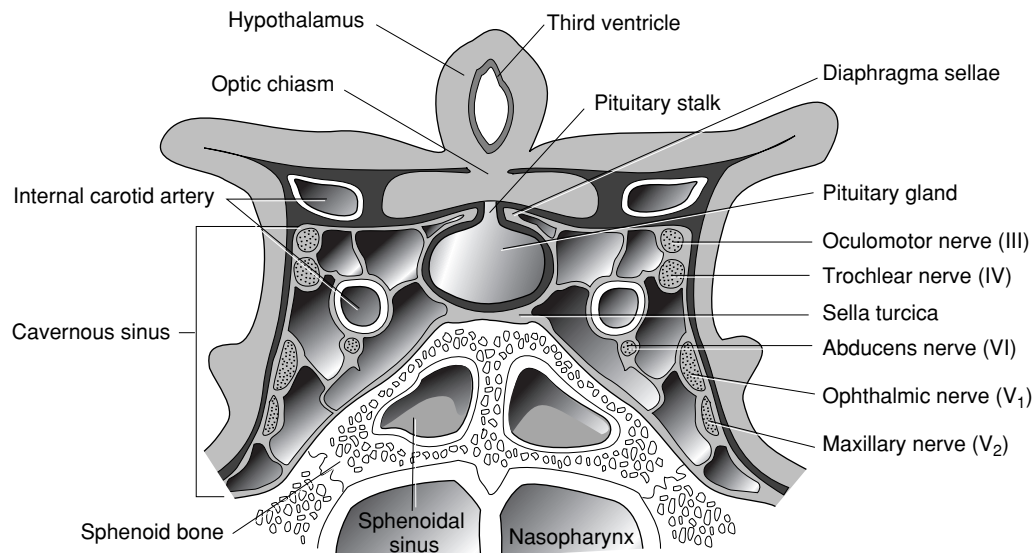
Cranial nerve and vessel pathways

Cribriform plate (CN I).	Divisions of CN V exit owing to Standing Room Only.
Middle cranial fossa (CN II–VI)—through sphenoid bone:	
1. Optic canal (CN II, ophthalmic artery, central retinal vein)	
2. Superior orbital fissure (CN III, IV, V ₁ , VI, ophthalmic vein)	
3. Foramen Rotundum (CN V ₂)	
4. Foramen Ovale (CN V ₃)	
5. Foramen spinosum (middle meningeal artery)	
Posterior cranial fossa (CN VII–XII)—through temporal or occipital bone:	
1. Internal auditory meatus (CN VII, VIII)	
2. Jugular foramen (CN IX, X, XI, jugular vein)	
3. Hypoglossal canal (CN XII)	
4. Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries)	

Cavernous sinus

A collection of venous sinuses on either side of the pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.
CN III, IV, V₁, V₂, and VI and postganglionic sympathetic fibers en route to the orbit all pass through the cavernous sinus. Only CN VI is “free-floating.” Cavernous portion of internal carotid artery is also here.

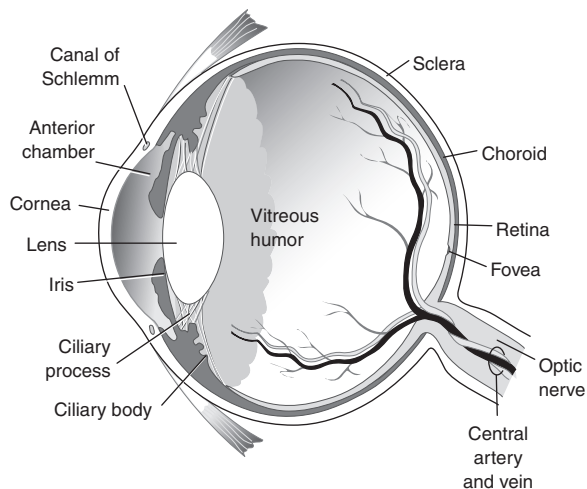
The nerves that control extraocular muscles (plus V₁ and V₂) pass through the cavernous sinus.
Cavernous sinus syndrome (e.g., due to mass effect)—ophthalmoplegia, ophthalmic and mandibular sensory loss.



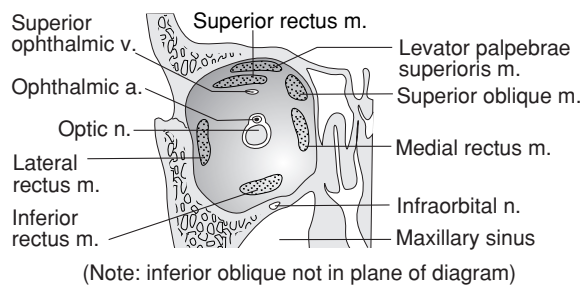
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:277.)

Mastication muscles	3 muscles close jaw: M asseter, t emporalis, M edial pterygoid. 1 opens: lateral pterygoid. All are innervated by the trigeminal nerve (V ₃).	M 's M unch. L ateral L owers (when speaking of pterygoids with respect to jaw motion).
Muscles with glossus	All muscles with root <i>glossus</i> in their names (except palatoglossus , innervated by vagus nerve) are innervated by hypoglossal nerve.	<i>Palat</i> : vagus nerve. <i>Glossus</i> : hypoglossal nerve.
Muscles with palat	All muscles with root <i>palat</i> in their names (except tensor veli palatini , innervated by mandibular branch of CN V) are innervated by vagus nerve.	<i>Palat</i> : vagus nerve (except TENSOR , who was too TENSE).

Eye and retina



Extraocular muscles and nerves



CN VI innervates the **Lateral Rectus**.

CN IV innervates the **Superior Oblique**.

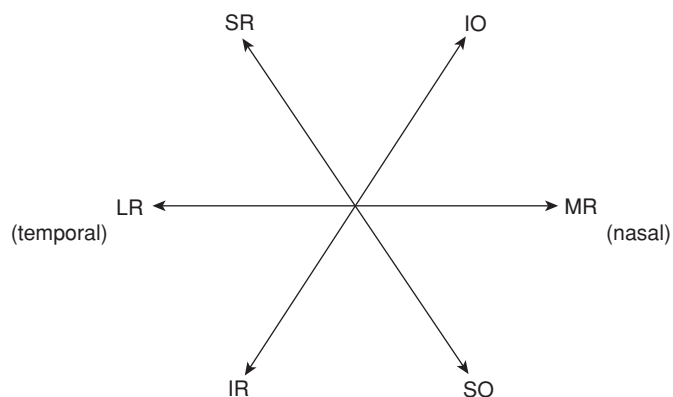
CN III innervates the **Rest**.

The “chemical formula”

LR₆SO₄R₃.

The superior oblique abducts, introverts, depresses.

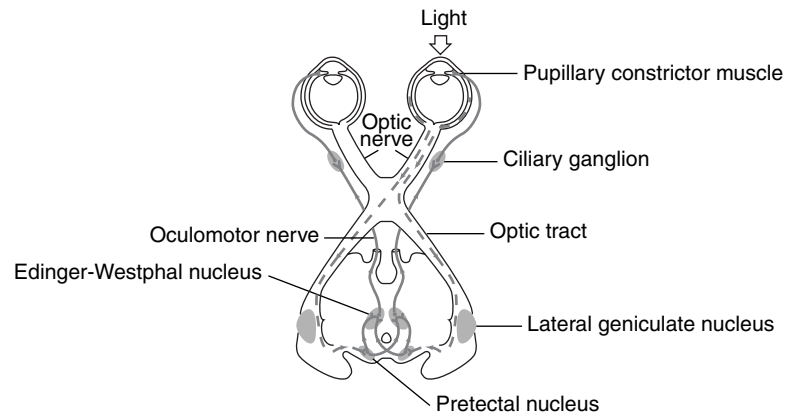
Direction of eye movements by extraocular muscles



Pupillary light reflex

Light in either retina sends a signal via CN III to pretectal nuclei (dashed lines) in midbrain that activate bilateral Edinger-Westphal nuclei; pupils contract bilaterally (consensual reflex).

Note that the illumination of 1 eye results in bilateral pupillary constriction.



(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 3rd ed. Stamford, CT: Appleton & Lange, 1996.)

KLM sounds: kuh, la, mi

Kuh-kuh-kuh tests palate elevation (CN X—vagus).
La-la-la tests tongue (CN XII—hypoglossal).
Mi-mi-mi tests lips (CN VII—facial).

Say it aloud.

Sleep stages

Stage (% of total sleep time in young adults)

Description

Awake (eyes open), alert, active mental concentration

Awake (eyes closed)

1 (5%)

Light sleep

2 (45%)

Deeper sleep

3–4 (25%)

Deepest, non-REM sleep; sleepwalking; night terrors, bed-wetting (slow-wave sleep)

REM (25%)

Dreaming, loss of motor tone, possibly a memory processing function, erections, ↑ brain O₂ use

Waveform

Beta (highest frequency, lowest amplitude)

Alpha

Theta

Sleep spindles and K complexes

Delta (lowest frequency, highest amplitude)

Beta

At night, **BATS Drink Blood**.

1. Serotonergic predominance of raphe nucleus key to initiating sleep
2. NE reduces REM sleep
3. Extraocular movements during REM due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center)
4. REM sleep having the same EEG pattern as while awake and alert has spawned the terms “paradoxical sleep” and “desynchronized sleep”
5. Benzodiazepines shorten stage 4 sleep; thus useful for night terrors and sleepwalking
6. Imipramine is used to treat enuresis because it ↓ stage 4 sleep

REM sleep

↑ and variable pulse, REM, ↑ and variable blood pressure, penile/clitoral tumescence. Occurs every 90 minutes; duration ↑ through the night. ACh is the principal neurotransmitter involved in REM sleep. REM sleep ↓ with age.

REM sleep is like sex:
↑ pulse, penile/
clitoral tumescence,
↓ with age.

Neural tube defects

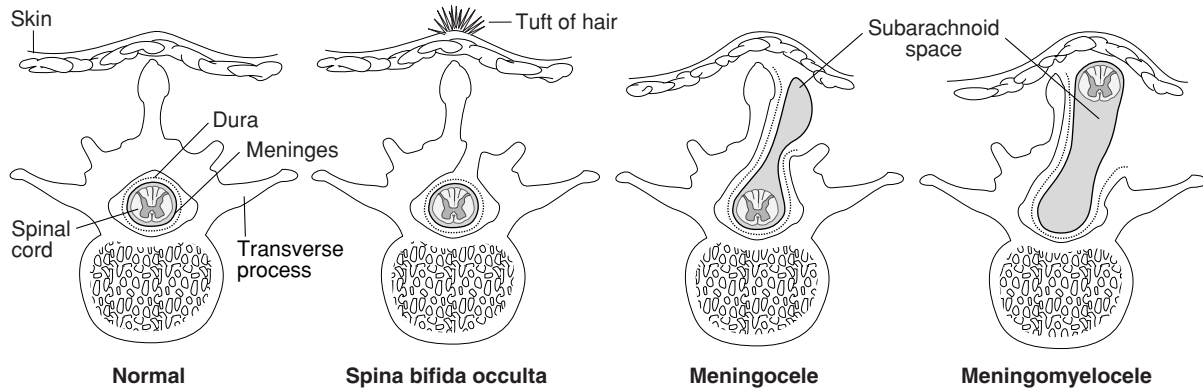
Associated with low folic acid intake during pregnancy. Elevated α -fetoprotein in amniotic fluid and maternal serum.

Spina bifida occulta—failure of bony spinal canal to close, but no structural herniation.

Usually seen at lower vertebral levels.

Meningocele—meninges herniate through spinal canal defect.

Meningomyelocele—meninges and spinal cord herniate through spinal canal defect.



Brain lesions

Area of lesion	Consequence	
Broca's area	Motor (nonfluent/expressive) aphasia with good comprehension	BRO ca's is BRO ken speech.
Wernicke's area	Sensory (fluent/receptive) aphasia with poor comprehension	Wernicke's is Wordy but makes no sense.
Arcuate fasciculus	Conduction aphasia; poor repetition with good comprehension, fluent speech	Connects Wernicke's to Broca's area.
Amygdala (bilateral)	Klüver-Bucy syndrome (hyperorality, hypersexuality, disinhibited behavior)	
Frontal lobe	Personality changes and deficits in concentration, orientation, and judgment; may have reemergence of primitive reflexes	
Right parietal lobe	Spatial neglect syndrome (agnosia of the contralateral side of the world)	
Reticular activating system	Coma	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome	
Basal ganglia	May result in tremor at rest, chorea, or athetosis	
Cerebellar hemisphere	Intention tremor, limb ataxia	Cerebellar hemispheres are laterally located—affect lateral limbs. Vermis is centrally located—affects central body.
Cerebellar vermis	Truncal ataxia, dysarthria	
Subthalamic nucleus	Contralateral hemiballismus	

Chorea

Sudden, jerky, purposeless movements. Characteristic of basal ganglia lesion (e.g., Huntington's disease).

Chorea = dancing (Greek). Think choral dancing or choreography.

Athetosis	Slow, writhing movements, especially of fingers. Characteristic of basal ganglia lesion.	<i>Athetos</i> = not fixed (Greek). Think snakelike.
Hemiballismus	Sudden, wild flailing of 1 arm. Characteristic of contralateral subthalamic nucleus lesion. Loss of inhibition of thalamus through globus pallidus.	Half ballistic (as in throwing a baseball).
Aphasia		
Broca's	Nonfluent aphasia with intact comprehension. Broca's area—inferior frontal gyrus.	Broca's is B roken speech; Wernicke's is W ordy but
Wernicke's	Fluent aphasia with impaired comprehension. Wernicke's area—superior temporal gyrus.	makes no sense. Wernicke's = "What?"
Degenerative diseases		
Cerebral cortex	Alzheimer's disease —most common cause of dementia in the elderly. Associated with senile plaques (extracellular, β -amyloid core) and neurofibrillary tangles (intracellular, abnormally phosphorylated tau protein). Familial form (10%) associated with genes on chromosomes 1, 14, 19 (<i>APOE4</i> allele), and 21 (<i>p-App</i> gene) (see Color Image 41). Pick's disease —dementia, aphasia, parkinsonian aspects; associated with Pick bodies (intracellular, aggregated tau protein) and is specific for the frontal and temporal lobes.	Multi-infarct dementia is the 2nd most common cause of dementia in the elderly. May cause amyloid angiopathy → intracranial hemorrhage.
Basal ganglia and brain stem	Huntington's disease —autosomal-dominant inheritance, chorea, dementia. Atrophy of caudate nucleus (loss of GABAergic neurons). Parkinson's disease —associated with Lewy bodies and depigmentation of the substantia nigra pars compacta (loss of dopaminergic neurons). Rare cases have been linked to exposure to MPTP, a contaminant in illicit street drugs.	Chromosome 4—expansion of CAG repeats. CAG —Caudate loses ACh and GABA . TRAP = Tremor (at rest), cogwheel Rigidity, Akinesia, and Postural instability (you are TRAP ped in your body).
Spinocerebellar Motor neuron	Olivopontocerebellar atrophy; Friedreich's ataxia. Amyotrophic lateral sclerosis (ALS) —associated with both LMN and UMN signs; no sensory deficit. Werdnig-Hoffmann disease —autosomal-recessive inheritance; presents at birth as a "floppy baby," tongue fasciculations; median age of death 7 months. Associated with degeneration of anterior horns. Polio —follows infection with poliovirus; LMN signs. Associated with degeneration of anterior horns.	Commonly known as Lou Gehrig's disease.

Poliomyelitis	Caused by poliovirus, which is transmitted by the fecal-oral route. Replicates in the oropharynx and small intestine before spreading through the bloodstream to the CNS, where it leads to the destruction of cells in the anterior horn of the spinal cord, leading in turn to LMN destruction.
Symptoms	Malaise, headache, fever, nausea, abdominal pain, sore throat. Signs of LMN lesions—muscle weakness and atrophy, fasciculations, fibrillation, and hyporeflexia.
Findings	CSF with lymphocytic pleocytosis with slight elevation of protein. Virus recovered from stool or throat.

Demyelinating and dysmyelinating diseases	<ol style="list-style-type: none"> 1. Multiple sclerosis (MS)—↑ prevalence with ↑ distance from the equator; periventricular plaques (areas of oligodendrocyte loss and reactive gliosis) with preservation of axons; ↑ protein (IgG) in CSF. Many patients have a relapsing-remitting course. Patients can present with optic neuritis (sudden loss of vision), MLF syndrome (internuclear ophthalmoplegia), hemiparesis, hemisensory symptoms, or bladder/bowel incontinence (see Color Image 47). 2. Progressive multifocal leukoencephalopathy (PML)—associated with JC virus and seen in 2–4% of AIDS patients (reactivation of latent viral infection). 3. Acute disseminated (postinfectious) encephalomyelitis. 4. Metachromatic leukodystrophy (a lysosomal storage disease). 5. Guillain-Barré syndrome (see below). 	<p>Classic triad of MS is a SIN:</p> <ul style="list-style-type: none"> Scanning speech Intention tremor Nystagmus <p>Most often affects women in their 20s and 30s; more common in whites.</p> <p>Treatment: β-interferon or immunosuppressant therapy.</p>
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Guillain-Barré syndrome (acute idiopathic polyneuritis)	<p>Inflammation and demyelination of peripheral nerves and motor fibers of ventral roots (sensory effect less severe than motor), causing symmetric ascending muscle weakness beginning in distal lower extremities. Facial diplegia in 50% of cases. Autonomic function may be severely affected (e.g., cardiac irregularities, hypertension, or hypotension). Almost all patients survive; the majority recover completely after weeks to months.</p> <p>Findings: elevated CSF protein with normal cell count (“albuminocytologic dissociation”). Elevated protein → papilledema.</p>	<p>Associated with infections → immune attack of peripheral myelin (e.g., herpesvirus or <i>Campylobacter jejuni</i> infection), inoculations, and stress, but no definitive link to pathogens.</p> <p>Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immune globulins.</p>
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Seizures	<p>Partial seizures—1 area of the brain.</p> <ol style="list-style-type: none"> 1. Simple partial (consciousness intact)—motor, sensory, autonomic, psychic 2. Complex partial (impaired consciousness) <p>Generalized seizures—diffuse.</p> <ol style="list-style-type: none"> 1. Absence (petit mal)—blank stare 2. Myoclonic—quick, repetitive jerks 3. Tonic-clonic (grand mal)—alternating stiffening and movement 4. Tonic—stiffening 5. Atonic—“drop” seizures 	<p>Epilepsy is a disorder of recurrent seizures (febrile seizures are not epilepsy). Partial seizures can secondarily generalize.</p> <p>Causes of seizures by age:</p> <p>Children—genetic, infection, trauma, congenital, metabolic.</p> <p>Adults—tumors, trauma, stroke, infection.</p> <p>Elderly—stroke, tumor, trauma, metabolic, infection.</p>
Intracranial hemorrhage	<p>Epidural hematoma Rupture of middle meningeal artery, often 2° to fracture of temporal bone. Lucid interval (see Color Image 44).</p> <p>Subdural hematoma Rupture of bridging veins. Venous bleeding (less pressure) with delayed onset of symptoms. Seen in elderly individuals, alcoholics, blunt trauma, shaken baby (predisposing factors—brain atrophy, shaking, whiplash) (see Color Image 43).</p> <p>Subarachnoid hemorrhage Rupture of an aneurysm (usually berry aneurysm) or an AVM. Patients complain of “worst headache of my life.” Bloody or xanthochromic spinal tap.</p> <p>Parenchymal hematoma Caused by hypertension, amyloid angiopathy, diabetes mellitus, and tumor.</p>	<p>CT shows “biconvex disk” not crossing suture lines.</p> <p>Crescent-shaped hemorrhage that crosses suture lines.</p>
Berry aneurysms	<p>Berry aneurysms occur at the bifurcations in the circle of Willis. Most common site is bifurcation of the anterior communicating artery. Rupture (most common complication) leads to hemorrhagic stroke/subarachnoid hemorrhage. Associated with adult polycystic kidney disease, Ehlers-Danlos syndrome, and Marfan’s syndrome. Other risk factors: advanced age, hypertension, smoking, race (higher risk in blacks) (see Color Image 46).</p>	

Primary brain tumors

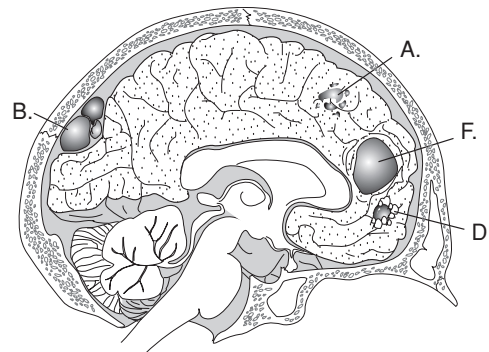
Clinical presentation due to mass effects (e.g., seizures, dementia, focal lesions); 1° brain tumors rarely undergo metastasis. The majority of adult 1° tumors are supratentorial, while the majority of childhood 1° tumors are infratentorial. Note: half of adult brain tumors are metastases.

Adult peak incidence

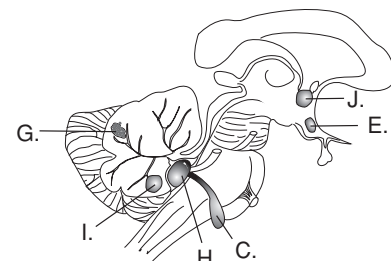
- | | | |
|---|--|---|
| A. Glioblastoma multiforme (grade IV astrocytoma) | Most common 1° brain tumor. Prognosis grave; < 1-year life expectancy. Found in cerebral hemispheres. Can cross corpus callosum (“butterfly glioma”) (see Color Image 48). Stain astrocytes with GFAP. | “Pseudopalisading” tumor cells—border central areas of necrosis and hemorrhage. |
| B. Meningioma | 2nd most common 1° brain tumor. Most often occurs in convexities of hemispheres and parasagittal region. Arises from arachnoid cells external to brain. Resectable. | Spindle cells concentrically arranged in a whorled pattern; psammoma bodies (laminated calcifications). |
| C. Schwannoma | 3rd most common 1° brain tumor. Schwann cell origin; often localized to 8th nerve → acoustic schwannoma. Resectable. | Bilateral schwannoma found in neurofibromatosis type 2. |
| D. Oligodendroglioma | Relatively rare, slow growing. Most often in frontal lobes (see Color Image 49). | Oligodendrocytes = “fried egg” cells—round nuclei with clear cytoplasm. Often calcified in oligodendroglioma. |
| E. Pituitary adenoma | Prolactin secreting is most common form. Bitemporal hemianopia (due to pressure on optic chiasm) and hyper- or hypopituitarism are sequelae. | Rathke’s pouch. |

Childhood peak incidence

- | | | |
|--------------------------------------|---|--|
| F. Pilocytic (low-grade) astrocytoma | Diffusely infiltrating glioma. In children, most often found in posterior fossa. Benign; good prognosis. | Rosenthal fibers—eosinophilic, corkscrew fibers. |
| G. Medulloblastoma | Highly malignant cerebellar tumor. A form of primitive neuroectodermal tumor (PNET). Can compress 4th ventricle, causing hydrocephalus. | Rosettes or perivascular pseudorosette pattern of cells. Radiosensitive. |
| H. Ependymoma | Ependymal cell tumors most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis. | Characteristic perivascular pseudorosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus. |
| I. Hemangioblastoma | Most often cerebellar; associated with von Hippel–Lindau syndrome when found with retinal angiomas. Can produce EPO → 2° polycythemia. | Foamy cells and high vascularity are characteristic. |
| J. Craniopharyngioma | Benign childhood tumor, confused with pituitary adenoma (can also cause bitemporal hemianopia). Most common childhood supratentorial tumor. | Derived from remnants of Rathke’s pouch. Calcification is common. |



Supratentorial



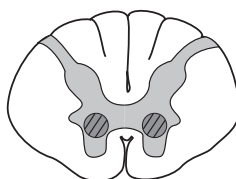
Infratentorial

Motor neuron signs

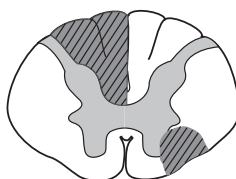
Sign	UMN lesion	LMN lesion	Lower MN = everything lowered (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes). Upper MN = everything up (tone, DTRs, toes).
Weakness	+	+	
Atrophy	—	+	
Fasciculation	—	+	
Reflexes	↑	↓	
Tone	↑	↓	
Babinski	+	—	

Spinal cord lesions

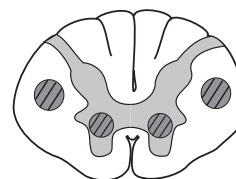
Poliomyelitis and Werdnig-Hoffmann disease: lower motor neuron lesions only, due to destruction of anterior horns; flaccid paralysis



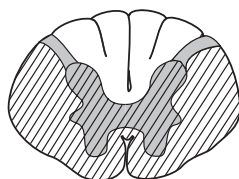
Multiple sclerosis: mostly white matter of cervical region; random and asymmetric lesions, due to demyelination; scanning speech, intention tremor, nystagmus



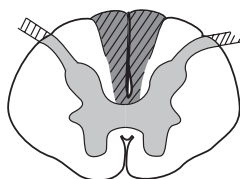
ALS: combined upper and lower motor neuron deficits with no sensory deficit; both upper and lower motor neuron signs



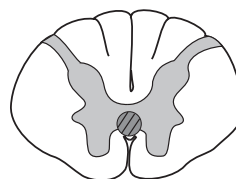
Complete occlusion of ventral artery; spares dorsal columns and tract of Lissauer



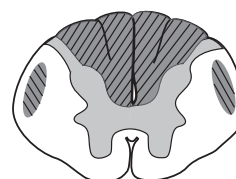
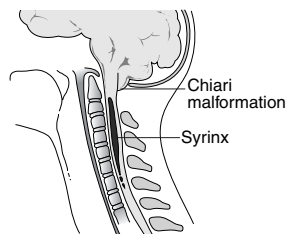
Tabes dorsalis (3° syphilis): degeneration of dorsal roots and dorsal columns; impaired proprioception, locomotor ataxia



Syringomyelia: crossing fibers of corticospinal tract damaged; bilateral loss of pain and temperature sensation

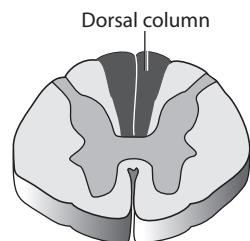


Vitamin B₁₂ neuropathy and Friedreich's ataxia: demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, hyperreflexia, impaired position and vibration sense

**Syringomyelia**

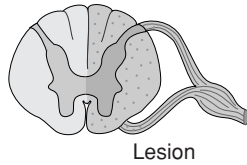
Enlargement of the central canal of spinal cord. Crossing fibers of spinothalamic tract are damaged. Bilateral loss of pain and temperature sensation in upper extremities with preservation of touch sensation.

Syrinx (Greek) = tube, as in syringe. Often presents in patients with Arnold-Chiari malformation. Most common at C8-T1.

Tabes dorsalis

Degeneration of dorsal columns and dorsal roots due to 3° syphilis, resulting in impaired proprioception and locomotor ataxia. Associated with Charcot's joints, shooting (lightning) pain, Argyll Robertson pupils (reactive to accommodation but not to light), and absence of DTRs.

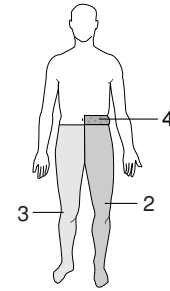
Brown-Séquard syndrome



Hemisection of spinal cord. Findings:

1. Ipsilateral UMN signs (corticospinal tract) below lesion—not shown
2. Ipsilateral loss of tactile, vibration, proprioception sense (dorsal column) below lesion
3. Contralateral pain and temperature loss (spinothalamic tract) below lesion
4. Ipsilateral loss of all sensation at level of lesion
5. LMN signs at level of lesion

If lesion occurs above T1, presents with Horner's syndrome.



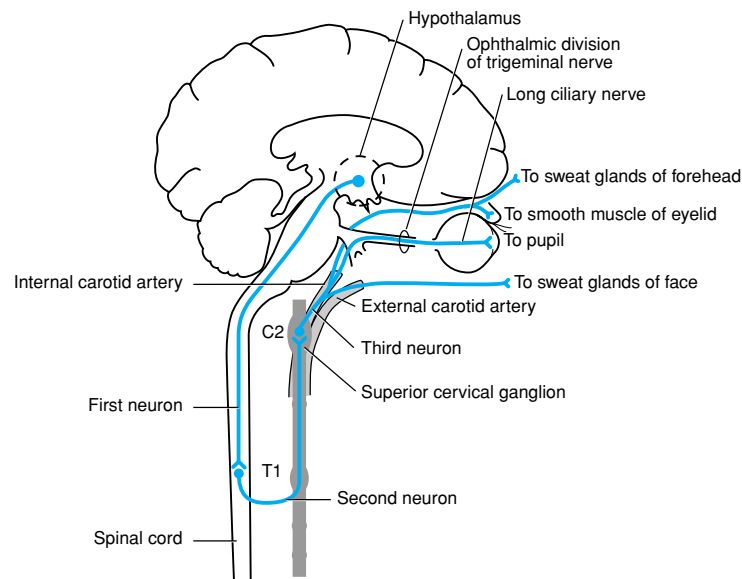
Horner's syndrome

Sympathectomy of face:

1. Ptosis (slight drooping of eyelid)
2. Anhidrosis (absence of sweating) and flushing (rubor) of affected side of face
3. Miosis (pupil constriction)

PAM is horny.

Associated with lesion of spinal cord above T1 (e.g., Pancoast's tumor, hemisection, late-stage syringomyelia).

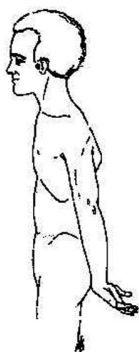


(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 4th ed. Stamford, CT: Appleton & Lange, 1999:146.)

The 3-neuron oculosympathetic pathway above projects from the hypothalamus to the intermediolateral column of the spinal cord, then to the superior cervical (sympathetic) ganglion, and finally to the pupil, the smooth muscle of the eyelids, and the sweat glands of the forehead and face. Interruption of these pathways results in Horner's syndrome.

Upper extremity nerve injury

Nerve	Site of injury/deficit in motion	Deficit in sensation/course
Radial	Shaft of humerus—loss of triceps brachii (triceps reflex), brachioradialis (brachioradialis reflex), and extensor carpi radialis longus (→ wrist drop).	Posterior brachial cutaneous. Posterior antebrachial cutaneous. Passes through supinator.
Median	Supracondyle of humerus—no loss of power in any of the arm muscles; loss of forearm pronation, wrist flexion, finger flexion, and several thumb movements; eventually, thenar atrophy.	Loss of sensation over the lateral palm and thumb and the radial 2½ fingers. Passes through pronator teres.
Ulnar	Medial epicondyle—impaired wrist flexion and adduction, and impaired adduction of thumb and the ulnar 2 fingers (→ claw hand).	Loss of sensation over the medial palm and ulnar 1½ fingers. Passes through flexor carpi ulnaris.
Axillary	Surgical neck of humerus or anterior shoulder dislocation—loss of deltoid action.	
Musculocutaneous	Loss of function of coracobrachialis, biceps, and brachialis muscles (biceps reflex).	Passes through coracobrachialis.

Erb-Duchenne palsy

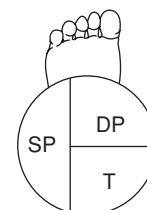
Traction or tear of the upper trunk of the brachial plexus (C5 and C6 roots); follows blow to shoulder or trauma during delivery.

Findings: limb hangs by side (paralysis of abductors), medially rotated (paralysis of lateral rotators), forearm is pronated (loss of biceps).

“Waiter’s tip” owing to appearance of arm.

Lower extremity nerve injury

Nerve	Deficit in motion	
Common peroneal (L4–S2)	Loss of dorsiflexion (→ foot drop). Deep peroneal nerve innervates anterior compartment; superficial peroneal nerve innervates lateral compartment.	PED = Peroneal Everts and Dorsiflexes; if injured, foot drop PED .
Tibial (L4–S3)	Loss of plantar flexion. Tibial nerve innervates posterior compartment.	TIP = Tibial Inverts and Plantarflexes; if injured, can’t stand on TIP toes.
Femoral (L2–L4)	Loss of knee extension/knee jerk.	
Obturator (L2–L4)	Loss of hip adduction.	



Thoracic outlet syndrome (Klumpke's palsy)

An embryologic defect; can compress subclavian artery and inferior trunk of brachial plexus (C8, T1), resulting in thoracic outlet syndrome:

1. Atrophy of the thenar and hypothenar eminences
2. Atrophy of the interosseous muscles
3. Sensory deficits on the medial side of the forearm and hand
4. Disappearance of the radial pulse upon moving the head toward the opposite side

Cranial nerve and cerebellar lesions

CN XII lesion (LMN)—tongue deviates **toward** side of lesion (lick your wounds).
 CN V motor lesion—jaw deviates **toward** side of lesion.
 Unilateral lesion of cerebellum—patient tends to fall **toward** side of lesion.
 CN X lesion—uvula deviates **away** from side of lesion.
 CN XI lesion—weakness turning head to contralateral side of lesion. Shoulder droop on side of lesion.

Facial lesions

UMN lesion

Lesion of motor cortex or connection between cortex and facial nucleus.
 Contralateral paralysis of lower face only.

LMN lesion

Ipsilateral paralysis of upper and lower face.

Bell's palsy

Complete destruction of the facial nucleus itself or its branchial efferent fibers (facial nerve proper).

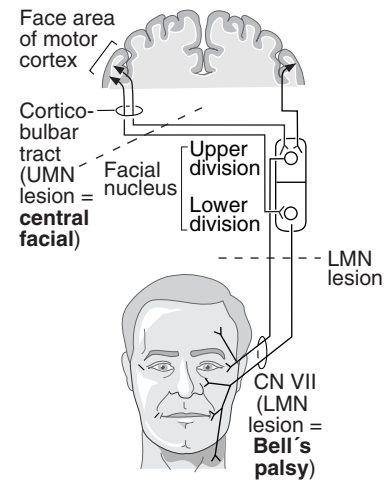
Peripheral ipsilateral facial paralysis with inability to close eye on involved side.

Can occur idiopathically; gradual recovery in most cases.

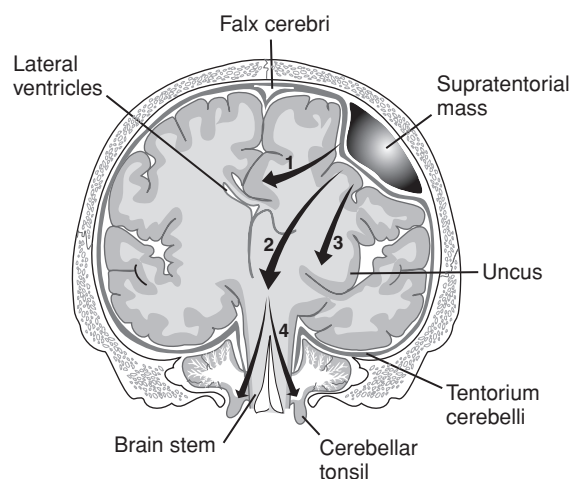
Seen as a complication in AIDS, Lyme disease, Sarcoidosis, Tumors, Diabetes.

ALexander Bell with STD:

AIDS, Lyme, Sarcoid, Tumors, Diabetes.



Herniation syndromes



1. Cingulate herniation under falx cerebri
2. Downward transtentorial (central) herniation
3. Uncal herniation
4. Cerebellar tonsillar herniation into the foramen magnum

Can compress anterior cerebral artery.
Coma and death result when these herniations compress the brain stem.
Uncus = medial temporal lobe.

(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 4th ed. Stamford, CT: Appleton & Lange, 1999:314.)

Uncal herniation

Clinical signs

Ipsilateral dilated pupil/ptosis

Contralateral homonymous hemianopia

Ipsilateral paresis

Duret

hemorrhages—
paramedian artery
rupture

Cause

Stretching of CN III

Compression of ipsilateral posterior cerebral artery

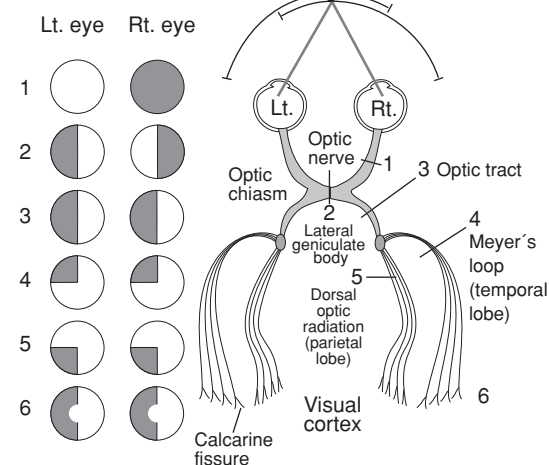
Compression of contralateral crus cerebri (Kernohan's notch)

Caudal displacement of brain stem

Visual field defects

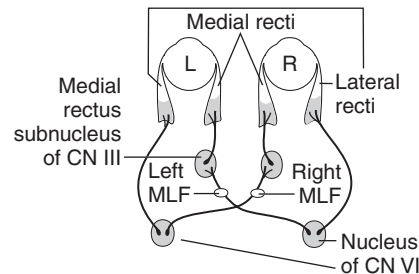
1. Right anopia
2. Bitemporal hemianopia
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion)
5. Left lower quadrantic anopia (right parietal lesion)
6. Left hemianopia with macular sparing

Defect in visual field of



**Internuclear
ophthalmoplegia
(MLF syndrome)**

Lesion in the medial longitudinal fasciculus (MLF).
Results in medial rectus palsy on attempted lateral gaze. Nystagmus in abducting eye. Convergence is normal. MLF syndrome is seen in many patients with multiple sclerosis.



MLF = MS.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

**Neurotransmitter
changes with
disease**

Anxiety—↑ NE, ↓ GABA, ↓ serotonin (5-HT).
Depression—↓ NE and ↓ serotonin (5-HT).
Alzheimer's dementia—↓ ACh.
Huntington's disease—↓ GABA, ↓ ACh.
Schizophrenia—↑ dopamine.
Parkinson's disease—↓ dopamine.

Orientation

Is the patient aware of him- or herself as a person?
Does the patient know his or her own name?
Anosognosia—unaware that one is ill.
Autotopagnosia—unable to locate one's own body parts.
Depersonalization—body seems unreal or dissociated.

Order of loss: 1st—time;
2nd—place; last—person.

Amnesia types

Anterograde amnesia is the inability to remember things that occurred after a CNS insult (no new memory).
Korsakoff's amnesia is a classic anterograde amnesia that is caused by thiamine deficiency (bilateral destruction of the mammillary bodies), is seen in alcoholics, and is associated with confabulations.
Retrograde amnesia is inability to remember things that occurred before a CNS insult.

Antero = after.

Retro = before.

**Substance
dependence**

Maladaptive pattern of substance use defined as 3 or more of the following signs in 1 year:

1. Tolerance
2. Withdrawal
3. Substance taken in larger amounts or over longer time than desired
4. Persistent desire or attempts to cut down
5. Significant energy spent obtaining, using, or recovering from substance
6. Important social, occupational, or recreational activities reduced because of substance use
7. Continued use in spite of knowing the problems that it causes

Substance abuse	<p>Maladaptive pattern leading to clinically significant impairment or distress. Symptoms have not met criteria for substance dependence. 1 or more of the following in 1 year:</p> <ol style="list-style-type: none"> 1. Recurrent use resulting in failure to fulfill major obligations at work, school, or home 2. Recurrent use in physically hazardous situations 3. Recurrent substance-related legal problems 4. Continued use in spite of persistent problems caused by use
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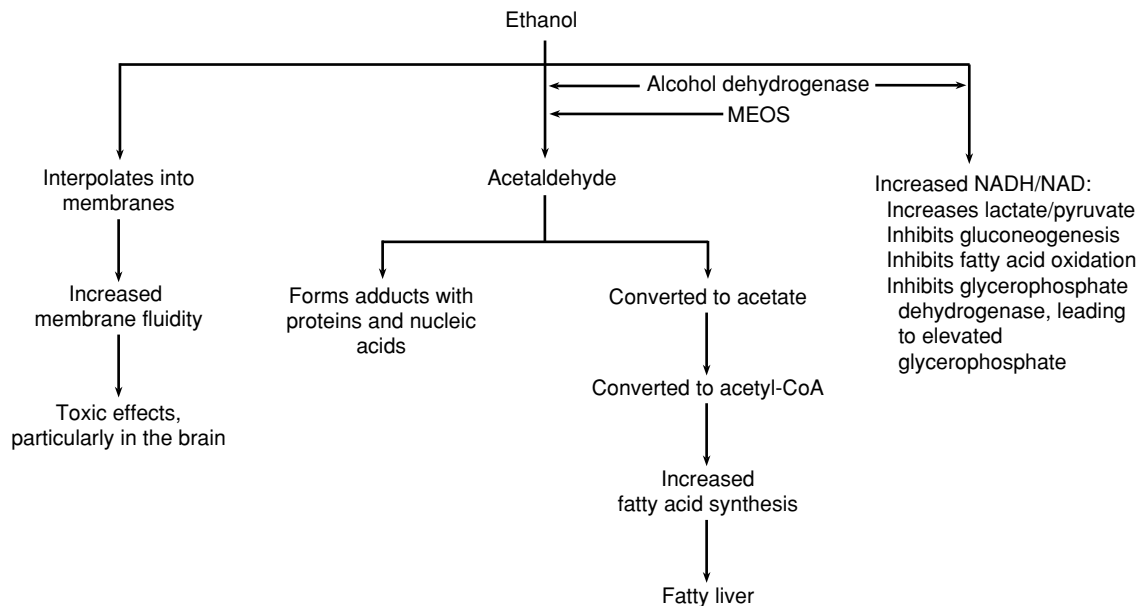
Signs and symptoms of substance abuse

Drug	Intoxication	Withdrawal
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ -glutamyltransferase (GGT)—sensitive indicator of alcohol use.	Tremor, tachycardia, hypertension, malaise, nausea, seizures, delirium tremens (DTs), tremulousness, agitation, hallucinations
Opioids	CNS depression, nausea and vomiting, constipation, pupillary constriction (pinpoint pupils), seizures (overdose is life-threatening).	Anxiety, insomnia, anorexia, sweating, dilated pupils, piloerection (“cold turkey”), fever, rhinorrhea, nausea, stomach cramps, diarrhea (“flulike” symptoms), yawning
Amphetamines	Psychomotor agitation, impaired judgment, pupillary dilation, hypertension, tachycardia, euphoria, prolonged wakefulness and attention, cardiac arrhythmias, delusions, hallucinations, fever.	Post-use “crash,” including depression, lethargy, headache, stomach cramps, hunger, hypersomnolence
Cocaine	Euphoria, psychomotor agitation, impaired judgment, tachycardia, pupillary dilation, hypertension, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death.	Post-use “crash,” including severe depression and suicidality, hypersomnolence, fatigue, malaise, severe psychological craving
PCP	Belligerence, impulsiveness, fever, psychomotor agitation, vertical and horizontal nystagmus, tachycardia, ataxia, homicidality, psychosis, delirium.	Recurrence of intoxication symptoms due to reabsorption in GI tract; sudden onset of severe, random, homicidal violence
LSD	Marked anxiety or depression, delusions, visual hallucinations, flashbacks, pupil dilation.	
Marijuana	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, \uparrow appetite, dry mouth, hallucinations.	
Barbiturates	Low safety margin, respiratory depression.	Anxiety, seizures, delirium, life-threatening cardiovascular collapse
Benzodiazepines	Greater safety margin. Amnesia, ataxia, somnolence, minor respiratory depression. Addictive effects with alcohol.	Rebound anxiety, seizures, tremor, insomnia
Caffeine	Restlessness, insomnia, increased diuresis, muscle twitching, cardiac arrhythmias.	Headache, lethargy, depression, weight gain
Nicotine	Restlessness, insomnia, anxiety, arrhythmias.	Irritability, headache, anxiety, weight gain, craving

Alcoholism

Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, delirium tremens) when intake is interrupted. Continued drinking despite medical and social contraindications and life disruptions.

Treatment: disulfiram to condition the patient to abstain from alcohol use. Supportive treatment of other systemic manifestations. Alcoholics Anonymous and other peer support groups are helpful in sustaining abstinence.



Delirium tremens

Life-threatening alcohol withdrawal syndrome that peaks 2–5 days after last drink. In order of appearance—autonomic system hyperactivity (tachycardia, tremors, anxiety), psychotic symptoms (hallucinations, delusions), confusion. Treat with benzodiazepines.

Complications of alcoholism

Alcoholic hepatitis and cirrhosis, pancreatitis, dilated cardiomyopathy, peripheral neuropathy, cerebellar degeneration, Wernicke-Korsakoff syndrome, testicular atrophy and hyperestrinism, and Mallory-Weiss syndrome.	
Alcoholic cirrhosis	Long-term alcohol use leads to micronodular cirrhosis with accompanying symptoms of jaundice, hypoalbuminemia, coagulation factor deficiencies, and portal hypertension, leading to peripheral edema and ascites, encephalopathy, neurologic manifestations (e.g., asterix, flapping tremor of the hands), and esophageal varices.
Wernicke-Korsakoff syndrome	Caused by vitamin B ₁ (thiamine) deficiency; common in malnourished alcoholics. Classically may present with triad of confusion, ophthalmoplegia, and ataxia (Wernicke's encephalopathy). May progress to memory loss, confabulation, personality change (Korsakoff's psychosis; irreversible). Associated with periventricular hemorrhage/necrosis, especially in mammillary bodies. Treatment: IV vitamin B ₁ (thiamine).
Mallory-Weiss syndrome	Longitudinal lacerations at the gastroesophageal junction caused by excessive vomiting. Associated with pain in contrast to esophageal varices.

Heroin addiction	<p>Approximately 500,000 U.S. addicts. Heroin is Schedule I (not prescribable). Look for track marks (needle sticks in veins).</p> <p>Users at risk for hepatitis, abscesses, overdose, hemorrhoids, AIDS, and right-sided endocarditis.</p>	<p>Naloxone (Narcan) and naltrexone competitively inhibit opioids.</p> <p>Methadone (long-acting oral opiate) for heroin detoxification or long-term maintenance.</p>
Delirium	<p>Rapid ↓ in attention span and level of arousal—disorganized thinking, hallucinations, illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction.</p> <p>Key to diagnosis: waxing and waning level of consciousness; develops rapidly.</p> <p>Often due to substance use/abuse or medical illness.</p>	<p>DeLiRIUM = changes in sensoRIUM.</p> <p>Most common psychiatric illness on medical and surgical floors. Often reversible.</p> <p>Check for drugs with anticholinergic effects.</p>
Dementia	<p>Gradual ↓ in cognition—memory deficits, aphasia, apraxia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment.</p> <p>Key to diagnosis: rule out delirium—patient is alert, no change in level of consciousness. More often gradual onset. In elderly patients, depression may present like dementia.</p>	<p>DeMEMtia characterized by MEMory loss. Commonly irreversible.</p>
Major depressive episode	<p>Characterized by at least 5 of the following for 2 weeks, including either depressed mood or anhedonia:</p> <ol style="list-style-type: none"> 1. Sleep disturbance 2. Loss of Interest (anhedonia) 3. Guilt or feelings of worthlessness 4. Loss of Energy 5. Loss of Concentration 6. Change in Appetite/weight 7. Psychomotor retardation or agitation 8. Suicidal ideations 9. Depressed mood <p>Lifetime prevalence of major depressive episode—5–12% male, 10–25% female.</p> <p>Major depressive disorder, recurrent—requires 2 or more episodes with a symptom-free interval of 2 months.</p> <p>Dysthymia is a milder form of depression lasting at least 2 years.</p>	<p>SIG E CAPS.</p>
Sleep patterns of depressed patients	<p>Patients with depression typically have the following changes in their sleep stages:</p> <ol style="list-style-type: none"> 1. ↓ slow-wave sleep 2. ↓ REM latency 3. Early-morning awakening (important screening question) 	

Risk factors for suicide completion	Sex (male), Age (teenager or elderly), Depression, Previous attempt, Ethanol or drug use, loss of Rational thinking, Sickness (medical illness, 3 or more prescription medications), Organized plan, No spouse (divorced, widowed, or single, especially if childless), Social support lacking. Women try more often; men succeed more often.	SAD PERSONS.
Electroconvulsive therapy	Treatment option for major depressive disorder refractory to other treatment. ECT is painless and produces a seizure. The major adverse effects of ECT are disorientation and anterograde and retrograde amnesia. Complications can result from anesthesia.	
Manic episode	Distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week. During mood disturbance, 3 or more of the following are present: <ol style="list-style-type: none"> 1. Distractibility 2. Irresponsibility—seeks pleasure without regard to consequences 3. Grandiosity—inflated self-esteem 4. Flight of ideas—racing thoughts 5. ↑ in goal-directed Activity/psychomotor Agitation 6. ↓ need for Sleep 7. Talkativeness or pressured speech 	DIG FAST.
Hypomanic episode	Like manic episode except mood disturbance not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization; there are no psychotic features.	
Bipolar disorder	6 separate criteria sets exist for bipolar disorders with combinations of manic (bipolar I), hypomanic (bipolar II), and depressed episodes. 1 manic or hypomanic episode defines bipolar disorder. Lithium is drug of choice. Cyclothymic disorder is a milder form lasting at least 2 years.	
Malingering	Patient consciously fakes or claims to have a disorder in order to attain a specific gain (e.g., avoiding work, obtaining drugs).	
Factitious disorder	Consciously creates symptoms in order to assume “sick role” and to get medical attention. Munchausen’s syndrome is manifested by a chronic history of multiple hospital admissions and willingness to receive invasive procedures. Munchausen’s syndrome by proxy is seen when illness in a child is caused by the parent. Motivation is unconscious. Is a form of child abuse and must be reported.	

Somatoform disorders	<p>Both illness production and motivation are unconscious drives. More common in women.</p> <p>Several types:</p> <ol style="list-style-type: none"> 1. Conversion—motor or sensory symptoms (e.g., paralysis, pseudoseizure) that suggest neurologic or physical disorder, but tests and physical exam are negative; often follows an acute stressor; patient may be unconcerned about symptoms 2. Somatoform pain disorder—prolonged pain that is not explained completely by illness 3. Hypochondriasis—preoccupation with and fear of having a serious illness in spite of medical reassurance 4. Somatization disorder—variety of complaints in multiple organ systems with no identifiable underlying physical findings 5. Body dysmorphic disorder—preoccupation with minor or imagined physical flaws; patients often seek cosmetic surgery 6. Pseudocyesis—false belief of being pregnant associated with objective physical signs of pregnancy 	
Gain: 1°, 2°, 3°	<p>1° gain—what the symptom does for the patient's internal psychic economy.</p> <p>2° gain—what the symptom gets the patient (sympathy, attention).</p> <p>3° gain—what the caretaker gets (like an MD on an interesting case).</p>	
Panic disorder	<p>Recurrent periods of intense fear and discomfort peaking in 10 minutes with 4 of the following: Palpitations, Paresthesias, Abdominal distress, Nausea, Intense fear of dying or losing control, lightheadedness, Chest pain, Chills, Choking, disconnectedness, Sweating, Shaking, Shortness of breath.</p> <p>Panic is described in context of occurrence (e.g., panic disorder with agoraphobia). High incidence during Step 1 exam.</p>	PANICS.
Specific phobia	<p>Fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation. Exposure provokes anxiety response. Person recognizes fear is excessive (insight). Fear interferes with normal routine. Treatment options include systematic desensitization. Examples include:</p> <ol style="list-style-type: none"> 1. Gamophobia (<i>gam</i> = gamete)—fear of marriage 2. Algophobia (<i>alg</i> = pain)—fear of pain 3. Acrophobia (<i>acro</i> = height)—fear of heights 4. Agoraphobia (<i>agora</i> = open market)—fear of open places 	
Post-traumatic stress disorder	<p>Person experienced or witnessed event that involved actual or threatened death or serious injury. Response involves intense fear, helplessness, or horror. Traumatic event is persistently reexperienced as nightmares or flashbacks; person persistently avoids stimuli associated with the trauma and experiences persistent symptoms of increased arousal. Disturbance lasts > 1 month and causes distress or social/occupational impairment. PTSD often follows acute stress disorder, which lasts up to 2–4 weeks.</p>	

Other anxiety disorders

Adjustment disorder—emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (e.g., divorce, moving) and lasting < 6 months.

Generalized anxiety disorder—uncontrollable anxiety for at least 6 months that is unrelated to a specific person, situation, or event. Sleep disturbance, fatigue, and difficulty concentrating are common.

Childhood and early-onset disorders

Autistic disorder—patients have severe communication problems and difficulty forming relationships. Characterized by repetitive behavior, unusual abilities (savants), and usually below-normal intelligence. Treatment: ↑ communication and social skills.

Asperger disorder—a milder form of autism involving problems with social relationships and repetitive behavior. Children are of normal intelligence and lack social or cognitive deficits.

Rett disorder—X-linked disorder seen only in girls (affected males die in utero). Characterized by loss of development and mental retardation appearing at approximately age 4. Stereotyped hand-wringing.

Attention-deficit hyperactivity disorder (ADHD)—limited attention span and hyperactivity. Children are emotionally labile, impulsive, and prone to accidents. Normal intelligence. Treatment: methylphenidate (Ritalin).

Conduct disorder—continued behavior violating social norms. At > 18 years of age, diagnosed as antisocial personality disorder.

Oppositional defiant disorder—child is noncompliant in the absence of criminality.

Tourette's syndrome—motor/vocal tics and involuntary profanity. Onset < 18 years. Treatment: haloperidol.

Separation anxiety disorder—fear of loss of attachment figure leading to factitious physical complaints to avoid going to school. Common onset age 7–8.

Eating disorders

Anorexia nervosa—abnormal eating habits (excessive dieting), body image distortion, and ↑ exercise. Severe weight loss, amenorrhea, anemia, and electrolyte disturbances can follow. Seen primarily in adolescent girls. Commonly coexists with depression.

Bulimia nervosa—binge eating followed by self-induced vomiting or use of laxatives. Body weight is normal. Parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from inducing vomiting.

Hallucination vs. illusion vs. delusion

Hallucinations are perceptions in the absence of external stimuli.

Illusions are misinterpretations of actual external stimuli.

Delusions are false beliefs not shared with other members of culture/subculture that are firmly maintained in spite of obvious proof to the contrary.

Delusion vs. loose association

A delusion is a disorder in the content of thought (the actual idea).

A loose association is a disorder in the form of thought (the way ideas are tied together).

Hallucination types	<p>Visual and auditory hallucinations are common in schizophrenia.</p> <p>Olfactory hallucination often occurs as an aura of a psychomotor epilepsy.</p> <p>Gustatory hallucination is rare.</p> <p>Tactile hallucination (e.g., formication—the sensation of ants crawling on one's skin) is common in DTs. Also seen in cocaine abusers (“cocaine bugs”).</p> <p>Hypnagogic hallucination occurs while GOing to sleep.</p> <p>Hypnopompic hallucination occurs while waking from sleep.</p>	
Sleep apnea	<p>Person stops breathing for at least 10 seconds repeatedly during sleep.</p> <p>Central sleep apnea—no respiratory effort.</p> <p>Obstructive sleep apnea—respiratory effort against airway obstruction.</p> <p>Associated with obesity, loud snoring, systemic/pulmonary hypertension, arrhythmias, and possibly sudden death.</p> <p>Individuals may become chronically tired.</p>	<p>Treatment: weight loss, CPAP, surgery.</p>
Narcolepsy	<p>Disordered regulation of sleep-wake cycles. May include hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations. The person's nocturnal and narcoleptic sleep episodes start off with REM sleep. Cataplexy (loss of all muscle tone following a strong emotional stimulus) in some patients. Strong genetic component.</p> <p>Treat with stimulants (e.g., amphetamines).</p>	
Schizophrenia	<p>Periods of psychosis and disturbed behavior with a decline in functioning lasting > 6 months (1–6 months—schizophreniform disorder; < 1 month—brief psychotic disorder, usually stress related).</p> <p>Diagnosis requires 2 or more of the following (1–4 are “positive symptoms”):</p> <ol style="list-style-type: none"> 1. Delusions 2. Hallucinations—often auditory 3. Disorganized thought (loose associations) 4. Disorganized or catatonic behavior 5. “Negative symptoms”—flat affect, social withdrawal, lack of motivation, lack of speech or thought <p>Genetic factors outweigh environmental factors in the etiology of schizophrenia.</p> <p>Lifetime prevalence—1.5% (males = females, blacks = whites). Presents earlier in men.</p>	<p>5 subtypes:</p> <ol style="list-style-type: none"> 1. Disorganized 2. Catatonic 3. Paranoid 4. Undifferentiated 5. Residual <p>Schizoaffective disorder—a combination of schizophrenia and a mood disorder.</p>

Personality	<p>Personality trait—an enduring pattern of perceiving, relating to, and thinking about the environment and oneself that is exhibited in a wide range of important social and personal contexts.</p> <p>Personality disorder—when these patterns become inflexible and maladaptive, causing impairment in social or occupational functioning or subjective distress; person is usually not aware of problem. Disordered patterns must be stable by early adulthood; not usually diagnosed in children.</p>	
Cluster A personality disorders	<p>Odd or eccentric; cannot develop meaningful social relationships. No psychosis; genetic association with schizophrenia.</p> <p>Types:</p> <ol style="list-style-type: none"> 1. Paranoid—distrust and suspiciousness; projection is main defense mechanism 2. Schizoid—voluntary social withdrawal, limited emotional expression 3. Schizotypal—interpersonal awkwardness, odd beliefs or magical thinking, eccentric appearance 	“Weird.”
Cluster B personality disorders	<p>Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.</p> <p>Types:</p> <ol style="list-style-type: none"> 1. Antisocial—disregard for and violation of rights of others, criminality; males > females; conduct disorder if < 18 years 2. Borderline—unstable mood and interpersonal relationships, impulsiveness, sense of emptiness; females > males 3. Histrionic—excessive emotionality, attention seeking, sexually provocative 4. Narcissistic—grandiosity, sense of entitlement; may react to criticism with rage; may demand “top” physician/best health care 	“Wild.”
Cluster C personality disorders	<p>Anxious or fearful; genetic association with anxiety disorders.</p> <p>Types:</p> <ol style="list-style-type: none"> 1. Avoidant—sensitive to rejection, socially inhibited, timid, feelings of inadequacy 2. Obsessive-compulsive—preoccupation with order, perfectionism, and control 3. Dependent—submissive and clinging, excessive need to be taken care of, low self-confidence 	“Worried.”

Parkinson's disease drugs Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.

Strategy	Agents	BALSA:
Agonize dopamine receptors	Bromocriptine (ergot alkaloid and partial dopamine agonist), pramipexole, ropinirole	Bromocriptine
Increase dopamine	Amantadine (may ↑ dopamine release)	Amantadine
	L-dopa/carbidopa (converted to dopamine in CNS)	Levodopa (with carbidopa)
Prevent dopamine breakdown	Selegiline (selective MAO type B inhibitor); entacapone, tolcapone (COMT inhibitors)	Selegiline (and COMT inhibitors)
Curb excess cholinergic activity	Benztrapine (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia)	Antimuscarinics

L-dopa (levodopa)/carbidopa

Mechanism	↑ level of dopamine in brain. Unlike dopamine, L-dopa can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine.
Clinical use	Parkinsonism.
Toxicity	Arrhythmias from peripheral conversion to dopamine. Carbidopa, a peripheral decarboxylase inhibitor, is given with L-dopa in order to ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects. Long-term use can → dyskinesia following administration, akinesia between doses.

Selegiline

Mechanism	Selectively inhibits MAO-B, thereby ↑ the availability of dopamine.
Clinical use	Adjunctive agent to L-dopa in treatment of Parkinson's disease.
Toxicity	May enhance adverse effects of L-dopa.

Sumatriptan

Mechanism	5-HT _{1D} agonist. Causes vasoconstriction. Half-life < 2 hours.
Clinical use	Acute migraine, cluster headache attacks.
Toxicity	Coronary vasospasm, mild tingling (contraindicated in patients with CAD or Prinzmetal's angina).

Epilepsy drugs

	PARTIAL		GENERALIZED			Mechanism	Notes
	Simple	Complex	Tonic-Clonic	Absence	Status		
Phenytoin	✓	✓	1st line		1st line for prophylaxis	↑ Na ⁺ channel inactivation	
Carbamazepine	✓	✓	1st line			↑ Na ⁺ channel inactivation	1st line for trigeminal neuralgia
Lamotrigine	✓	✓	✓			Blocks voltage-gated Na ⁺ channels	
Gabapentin	✓	✓	✓			↑ GABA release	Also used for peripheral neuropathy
Topiramate	✓	✓	✓			Blocks Na ⁺ channels, ↑ GABA action	
Phenobarbital	✓	✓	✓			↑ GABA _A action	1st line in pregnant women, children
Valproic acid	✓	✓	1st line	✓		↑ Na ⁺ channel inactivation, ↑ GABA concentration	Also used for myoclonic seizures
Ethosuximide				1st line		Blocks thalamic T-type Ca ²⁺ channels	
Benzodiazepines (diazepam or lorazepam)					1st line for acute	↑ GABA _A action	Also used for seizures of eclampsia (1st line to prevent seizures of eclampsia is MgSO ₄)

Epilepsy drug toxicities

Benzodiazepines	Sedation, tolerance, dependence.
Carbamazepine	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450.
Ethosuximide	GI distress, lethargy, headache, urticaria, Stevens-Johnson syndrome.
Phenobarbital	Sedation, tolerance, dependence, induction of cytochrome P-450.
Phenytoin	Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, megaloblastic anemia, teratogenesis, SLE-like syndrome, induction of cytochrome P-450.
Valproic acid	GI distress, rare but fatal hepatotoxicity (measure LFTs), neural tube defects in fetus (spina bifida), tremor, weight gain.
Lamotrigine	Stevens-Johnson syndrome.
Gabapentin	Sedation, ataxia.
Topiramate	Sedation, mental dulling, kidney stones, weight loss.

Phenytoin		
Mechanism	Use-dependent blockade of Na ⁺ channels; inhibition of glutamate release from excitatory presynaptic neuron.	
Clinical use	Tonic-clonic seizures. Also a class IB antiarrhythmic.	
Toxicity	Nystagmus, ataxia, diplopia, sedation, SLE-like syndrome, induction of cytochrome P-450. Chronic use produces gingival hyperplasia in children, peripheral neuropathy, hirsutism, megaloblastic anemia (↓ vitamin B ₁₂), and malignant hyperthermia (rare); teratogenic (fetal hydantoin syndrome).	
<hr/>		
Barbiturates		
Mechanism	Phenobarbital, pentobarbital, thiopental, secobarbital. Facilitate GABA _A action by ↑ duration of Cl ⁻ channel opening, thus ↓ neuron firing.	Barbi DURATe (increased DURATion).
Clinical use	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).	Contraindicated in porphyria.
Toxicity	Dependence, additive CNS depression effects with alcohol, respiratory or cardiovascular depression (can lead to death), drug interactions owing to induction of liver microsomal enzymes (cytochrome P-450). Treat overdose with symptom management (assist respiration, ↑ BP).	
<hr/>		
Benzodiazepines		
Mechanism	Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam. Facilitate GABA _A action by ↑ frequency of Cl ⁻ channel opening. Most have long half-lives and active metabolites.	FR enzodiazepines (increased FR equency).
Clinical use	Anxiety, spasticity, status epilepticus (lorazepam and diazepam), detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking.	Short acting = TOM Thumb = Triazolam, Oxazepam, Midazolam .
Toxicity	Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA receptor).	

**Antipsychotics
(neuroleptics)**

	Thioridazine, haloperidol, fluphenazine, chlorpromazine.	
Mechanism	Most antipsychotics block dopamine D₂ receptors (excess dopamine effects connected with schizophrenia).	Evolution of EPS side effects: 4 h acute dystonia 4 d akinesia 4 wk akathisia 4 mo tardive dyskinesia (often irreversible)
Clinical use	Schizophrenia, psychosis, acute mania, Tourette syndrome	
Toxicity	Extrapyramidal system (EPS) side effects, endocrine side effects (e.g., dopamine receptor antagonism → hyperprolactinemia → gynecomastia), and side effects arising from blocking muscarinic (dry mouth, constipation), α (hypotension), and histamine (sedation) receptors. Neuroleptic malignant syndrome —rigidity, myoglobinuria, autonomic instability, hyperpyrexia (treat with dantrolene and dopamine agonists). Tardive dyskinesia —stereotypic oral-facial movements probably due to dopamine receptor sensitization; results of long-term antipsychotic use.	

**Atypical
antipsychotics**

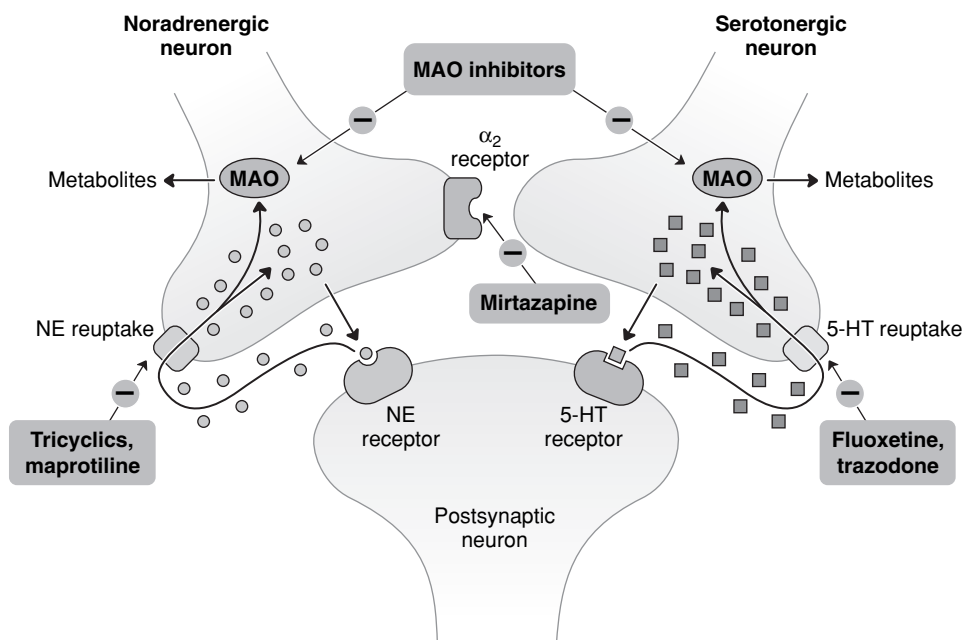
	Clozapine, olanzapine, risperidone.		It's not atypical for old closets to RISPER .
Mechanism	Block 5-HT ₂ and dopamine receptors.		
Clinical use	Treatment of schizophrenia; useful for positive and negative symptoms. Olanzapine is also used for OCD, anxiety disorder, depression, mania, Tourette syndrome.		
Toxicity	Fewer extrapyramidal and anticholinergic side effects than other antipsychotics. Clozapine may cause agranulocytosis (requires weekly WBC monitoring).		

Lithium

Mechanism	Not established; possibly related to inhibition of phosphoinositol cascade.	LMNOP:
Clinical use	Mood stabilizer for bipolar affective disorder; blocks relapse and acute manic events.	Lithium side effects— M ovement (tremor) N ephrogenic diabetes insipidus H ypOthyroidism P regnancy problems
Toxicity	Tremor, hypothyroidism, polyuria (ADH antagonist causing nephrogenic diabetes insipidus), teratogenesis. Narrow therapeutic window requiring close monitoring of serum levels.	

Antidepressants

1. SSRIs
2. Tricyclic antidepressants
3. Heterocyclic antidepressants
4. MAOIs



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:80.)

SSRIs	Fluoxetine, sertraline, paroxetine, citalopram.	
Mechanism	Serotonin-specific reuptake inhibitors.	
Clinical use	Endogenous depression, OCD.	It normally takes 2–3 weeks
Toxicity	Fewer than TCAs. GI distress, sexual dysfunction (anorgasmia). “Serotonin syndrome” with MAO inhibitors—hyperthermia, muscle rigidity, cardiovascular collapse.	for antidepressants to have an effect.
Tricyclic antidepressants	Imipramine, amitriptyline, desipramine, nortriptyline, clomipramine, doxepin.	
Mechanism	Block reuptake of NE and serotonin.	
Clinical use	Major depression, bedwetting (imipramine), OCD (clomipramine).	
Side effects	Sedation, α -blocking effects, atropine-like (anticholinergic) side effects (tachycardia, urinary retention). 3° TCAs (amitriptyline) have more anticholinergic effects than do 2° TCAs (nortriptyline). Desipramine is the least sedating.	
Toxicity	Tri-C’s: Convulsions, Coma, Cardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline).	

Heterocyclic antidepressants		2nd- and 3rd-generation antidepressants with varied and mixed mechanisms of action. Treat major depression.	
Bupropion		Also used for smoking cessation. Mechanism not well known. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizure in bulimic patients. Does not cause sexual side effects.	You need BU tane in your VEINs to MUR der for a MAP of Alca TRAZ .
Venlafaxine		Also used in generalized anxiety disorder. Inhibits serotonin, NE, and dopamine reuptake. Toxicity: stimulant effects, sedation, nausea, constipation, ↑ BP.	
Mirtazapine		α ₂ antagonist (↑ release of NE and serotonin) and potent 5-HT ₂ and 5-HT ₃ receptor antagonist. Toxicity: sedation, ↑ appetite, weight gain, dry mouth.	
Maprotiline		Blocks NE reuptake. Toxicity: sedation, orthostatic hypotension.	
Trazodone		Primarily inhibit serotonin reuptake. Toxicity: sedation, nausea, priapism, postural hypotension.	
Monoamine oxidase (MAO) inhibitors		Phenelzine, tranylcypromine.	
Mechanism		Nonselective MAO inhibition → ↑ levels of amine neurotransmitters.	
Clinical use		Atypical depression (i.e., with psychotic or phobic features), anxiety, hypochondriasis.	
Toxicity		Hypertensive crisis with tyramine ingestion (in many foods) and meperidine; CNS stimulation. Contraindication with SSRIs or β-agonists (to prevent serotonin syndrome).	
Anesthetics—general principles		CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported. Drugs with ↓ solubility in blood = rapid induction and recovery times. Drugs with ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$ where MAC = minimal anesthetic concentration. Examples: N ₂ O has low blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.	
Inhaled anesthetics		Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, nitrous oxide.	
Mechanism		Mechanism unknown. The lower the solubility in blood, the quicker the anesthetic induction and the quicker the recovery.	
Effects		Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).	
Toxicity		Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), malignant hyperthermia (rare).	

Intravenous anesthetics

Barbiturates	Thiopental—high potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by redistribution from brain. ↓ cerebral blood flow.
Benzodiazepines	Midazolam most common drug used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat with flumazenil), and amnesia.
Arylcyclohexamines (Ketamine)	PCP analogs that act as dissociative anesthetics. Cardiovascular stimulants. Cause disorientation, hallucination, and bad dreams. ↑ cerebral blood flow.
Opiates	Morphine, fentanyl used with other CNS depressants during general anesthesia.
Propofol	Used for rapid anesthesia induction and short procedures. Less postoperative nausea than thiopental.

B. B. King on OPIATES
PROPOses **FOOL**ishly.

Local anesthetics

	Esters—procaine, cocaine, tetracaine; amides— I doca I ne, mep I vaca I ne, bup I vaca I ne (am I des have 2 I 's in name).
Mechanism	Block Na ⁺ channels by binding to specific receptors on inner portion of channel. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form.
Principle	<ol style="list-style-type: none"> 1. In infected (acidic) tissue, anesthetics are charged and cannot penetrate membrane effectively. Therefore, more anesthetic is needed in these cases. 2. Order of nerve blockade—small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that very small unmyelinated pain fibers > small myelinated autonomic fibers > large myelinated autonomic fibers. Order of loss—pain (lose first) > temperature > touch > pressure (lose last). 3. Given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration.
Clinical use	Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.
Toxicity	CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, and arrhythmias (cocaine).

Neuromuscular blocking drugs

Depolarizing	Used for muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor. Succinylcholine. Reversal of blockade: Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors. Phase II (repolarized but blocked)—antidote consists of cholinesterase inhibitors (e.g., neostigmine).
Nondepolarizing	Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rapacuronium. Competitive—compete with ACh for receptors. Reversal of blockade—neostigmine, edrophonium, and other cholinesterase inhibitors.

Dantrolene

Used in the treatment of malignant hyperthermia, which is caused by the concomitant use of inhalation anesthetics (except N₂O) and succinylcholine. Also used to treat neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

Mechanism: prevents the release of Ca²⁺ from the sarcoplasmic reticulum of skeletal muscle.

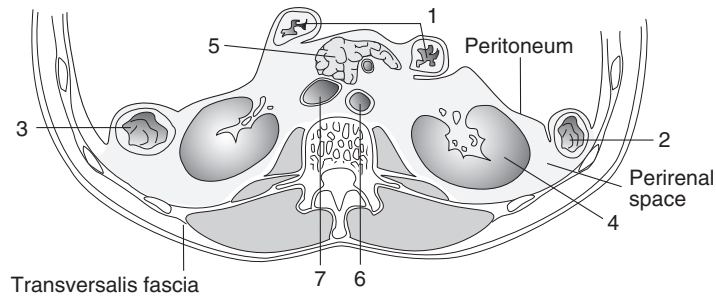
Renal

“But I know all about love already. I know precious little about kidneys.”
—Aldous Huxley, *Antic Hay*

“This too shall pass. Just like a kidney stone.”
—Hunter Madsen

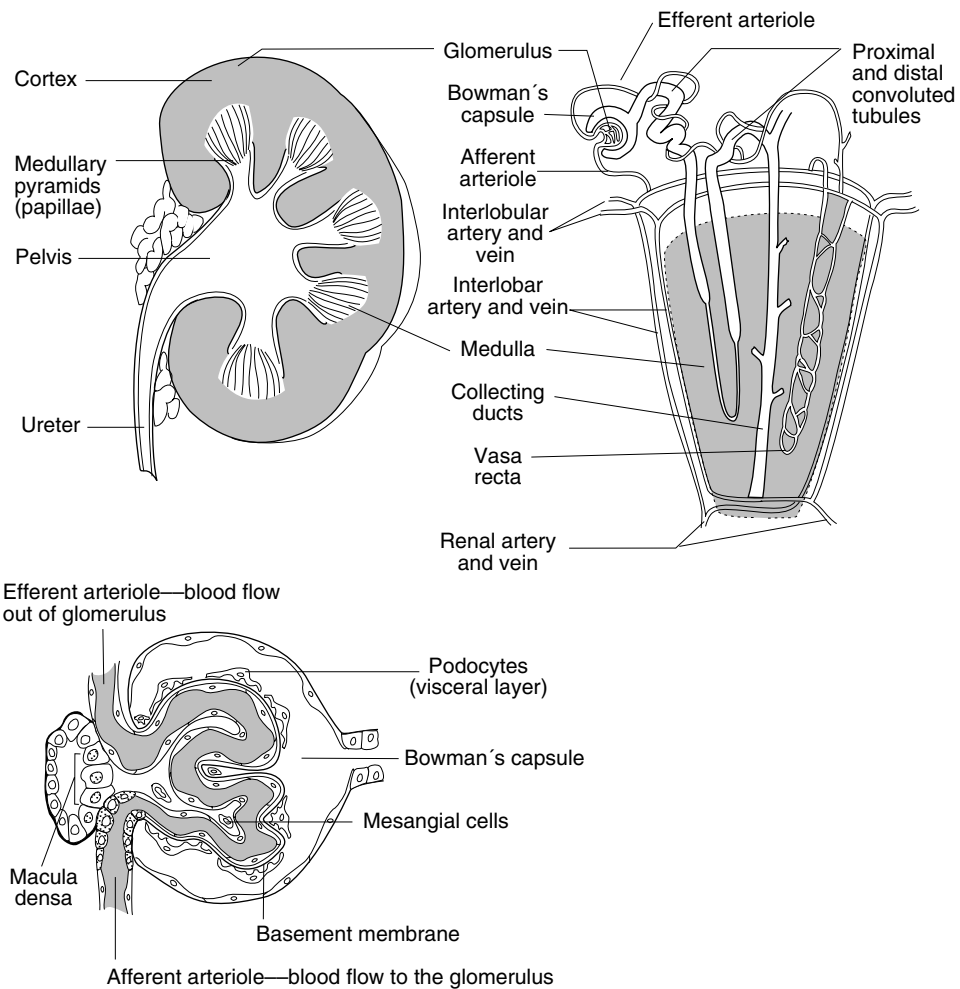
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

Retroperitoneal structures



1. Duodenum (2nd, 3rd, 4th parts)
 2. Descending colon
 3. Ascending colon
 4. Kidney and ureters
 5. Pancreas (except tail)
 6. Aorta
 7. IVC
- Adrenal glands and rectum (not shown in diagram)

Kidney anatomy and glomerular structure



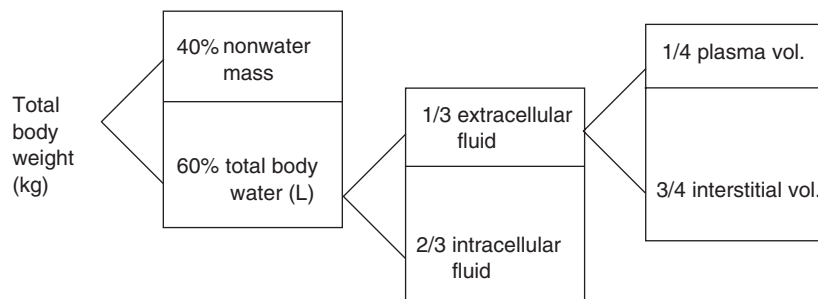
(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:384.)

Ureters: course

Ureters pass **under** uterine artery and **under** ductus deferens (retroperitoneal).

Water (ureters) **under** the bridge (artery, ductus deferens).

Fluid compartments



TBW – ECF = ICF.
 ECF – PV = interstitial volume.
 60–40–20 rule (% of body weight):
 60% total body water
 40% ICF
 20% ECF
 Plasma volume measured by radiolabeled albumin.
 Extracellular volume measured by inulin.

Renal clearance

$C_x = U_x V / P_x$ = volume of plasma from which the substance is cleared completely per unit time.
 If $C_x < \text{GFR}$, then there is net tubular reabsorption of X.
 If $C_x > \text{GFR}$, then there is net tubular secretion of X.
 If $C_x = \text{GFR}$, then there is no net secretion or reabsorption.

Be familiar with calculations.
 C_x = clearance of X.
 U_x = urine concentration of X.
 P_x = plasma concentration of X.
 V = urine flow rate.

Glomerular filtration barrier

Responsible for filtration of plasma according to size and net charge.
 Composed of:
 1. Fenestrated capillary endothelium (size barrier)
 2. Fused basement membrane with heparan sulfate (negative charge barrier)
 3. Epithelial layer consisting of podocyte foot processes

The charge barrier is lost in nephrotic syndrome, resulting in albuminuria, hypoproteinemia, generalized edema, and hyperlipidemia.

Glomerular filtration rate

Inulin can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$\text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}}$$

$$= K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$
 (GC = glomerular capillary; BS = Bowman's space.)
 π_{BS} normally equals zero.

Creatinine clearance is an approximate measure of GFR.

Effective renal plasma flow

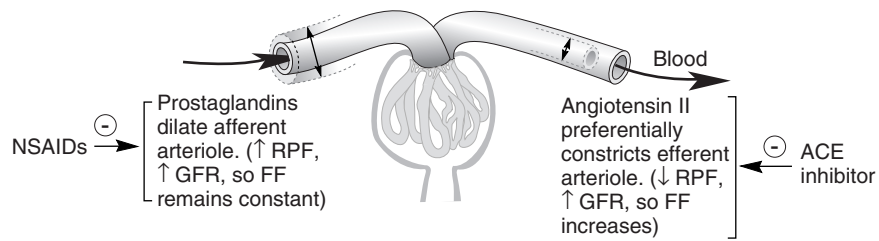
ERPF can be estimated using PAH because it is both filtered and actively secreted in the proximal tubule. All PAH entering the kidney is excreted.

$$\text{ERPF} = U_{\text{PAH}} \times V / P_{\text{PAH}} = C_{\text{PAH}}$$

$$\text{RBF} = \text{RPF} / (1 - \text{Hct})$$
 ERPF underestimates true RPF by ~10%.

Filtration fraction

$$FF = GFR/RPF.$$



Changes in renal function

Effect	RPF	GFR	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	NC
Efferent arteriole constriction	↓	↑	↑
↑ plasma protein concentration	NC	↓	↓
↓ plasma protein concentration	NC	↑	↑
Constriction of ureter	NC	↓	↓

Free water clearance

Given urine flow rate, urine osmolarity, and plasma osmolarity, be able to calculate free water clearance:

$$C_{H_2O} = V - C_{osm}.$$

$$V = \text{urine flow rate}; C_{osm} = U_{osm} V / P_{osm}.$$

Glucose clearance

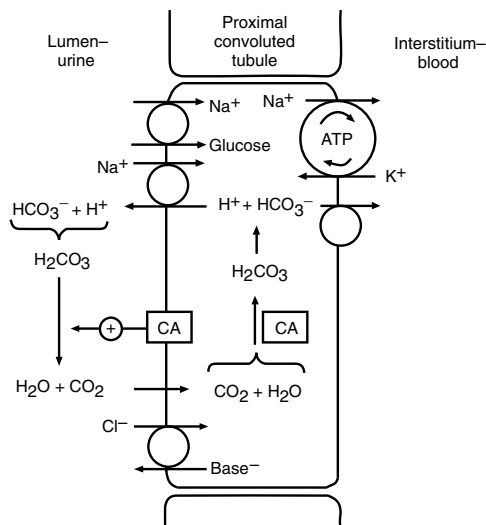
Glucose at a normal level is completely reabsorbed in proximal tubule. At plasma glucose of 200 mg/dL, glucosuria begins (threshold). At 350 mg/dL, transport mechanism is saturated (T_m).

Glucosuria is an important clinical clue to diabetes mellitus.

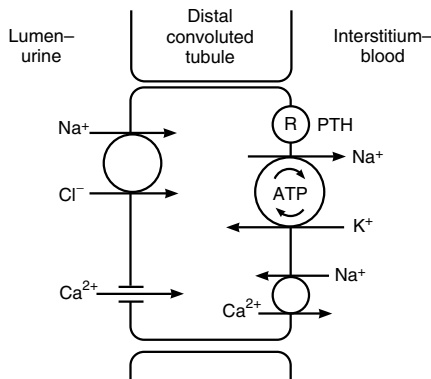
Amino acid clearance

Reabsorption by at least 3 distinct carrier systems, with competitive inhibition within each group. 2° active transport occurs in proximal tubule and is saturable.

Nephron physiology

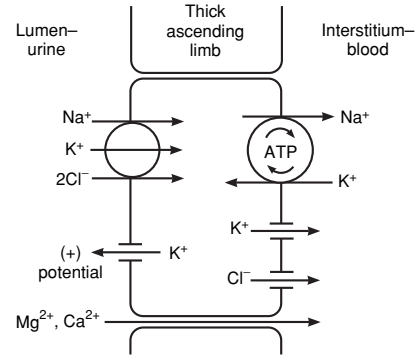


A. Early proximal convoluted tubule—"workhorse of the nephron." Reabsorbs all of the glucose and amino acids and most of the bicarbonate, sodium, and water. Secretes ammonia, which acts as a buffer for secreted H^+ .

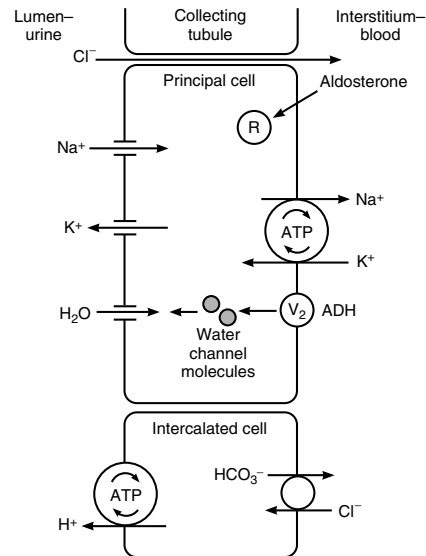


D. Early distal convoluted tubule—actively reabsorbs Na^+ , Cl^- . Reabsorption of Ca^{2+} is under the control of PTH.

B. Thin descending loop of Henle—passively reabsorbs water via medullary hypertonicity (impermeable to sodium).

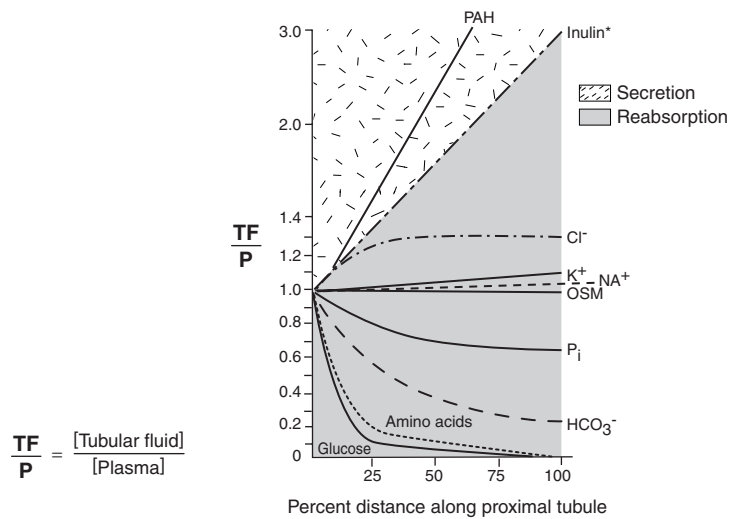


C. Thick ascending loop of Henle—actively reabsorbs Na^+ , K^+ , and Cl^- and indirectly induces the reabsorption of Mg^{2+} and Ca^{2+} . Impermeable to H_2O .



E. Collecting tubules—reabsorb Na^+ in exchange for secreting K^+ or H^+ (regulated by aldosterone). Reabsorption of water is regulated by ADH (vasopressin). Osmolarity of medulla can reach 1200 mOsm.

Relative concentrations along renal tubule



* Neither secreted nor reabsorbed; concentration increases as water is reabsorbed.

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

Renin-angiotensin system

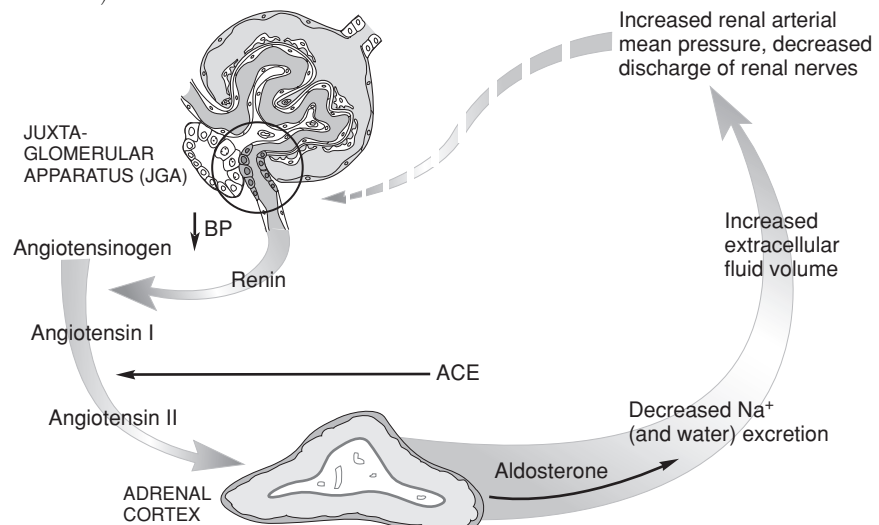
Mechanism

Renin is released by the kidneys upon sensing ↓ BP and cleaves angiotensinogen to angiotensin I (a decapeptide). Angiotensin I is then cleaved by angiotensin-converting enzyme (ACE), primarily in the lung capillaries and elsewhere, to angiotensin II (an octapeptide).

Actions of angiotensin II

1. Potent vasoconstriction
 2. Release of aldosterone from the adrenal cortex
 3. Release of ADH from posterior pituitary
 4. Stimulates hypothalamus → ↑ thirst
- Overall, angiotensin II serves to ↑ intravascular volume and ↑ BP.

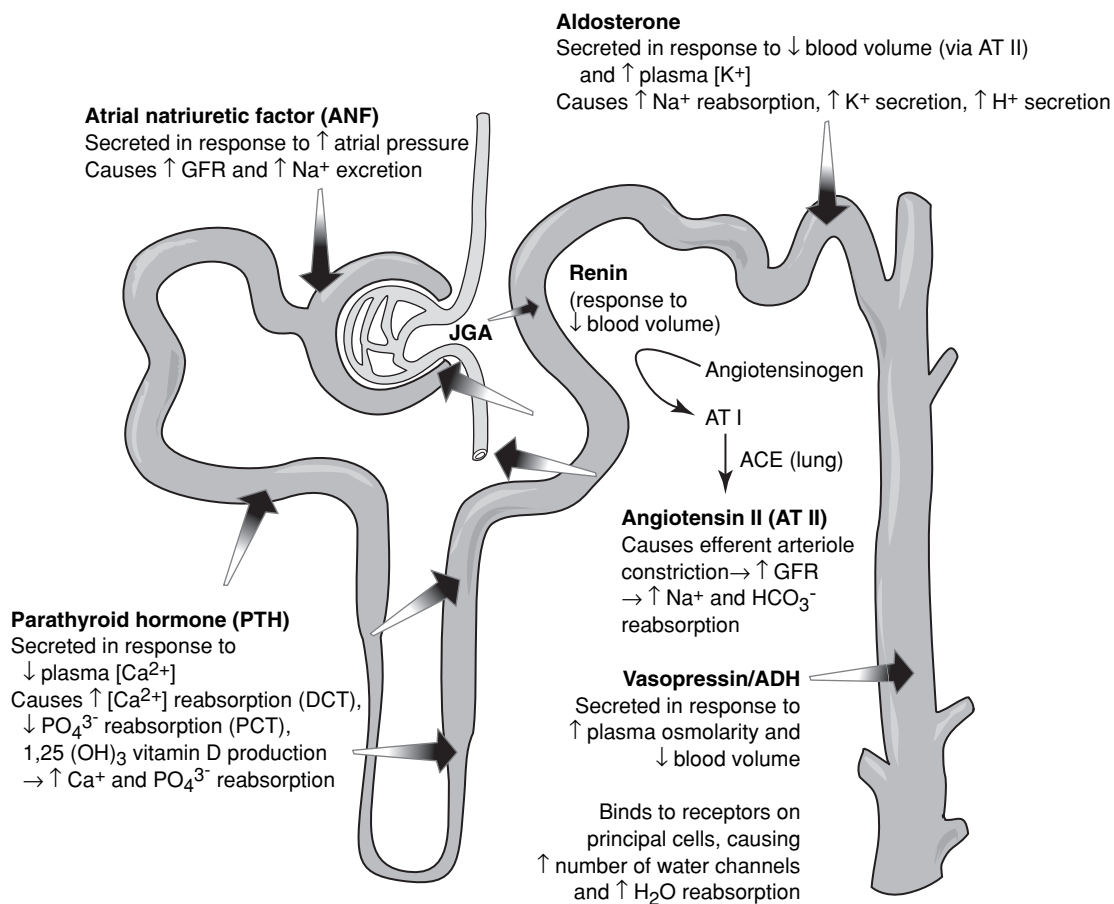
ANP released from atria may act as a “check” on the renin-angiotensin system (e.g., in heart failure).



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 20th ed. New York: McGraw-Hill, 2001.)

Juxtaglomerular apparatus (JGA)	JGA—JG cells (modified smooth muscle of afferent arteriole) and macula densa (Na^+ sensor, part of the distal convoluted tubule). JG cells secrete renin (leading to \uparrow angiotensin II and aldosterone levels) in response to \downarrow renal blood pressure, \downarrow Na^+ delivery to distal tubule, and \uparrow sympathetic tone.	JGA defends glomerular filtration rate via the renin-angiotensin system. <i>Juxta</i> = close by.
Kidney endocrine functions	<p>Endocrine functions of the kidney:</p> <ol style="list-style-type: none"> 1. Endothelial cells of peritubular capillaries secrete erythropoietin in response to hypoxia 2. Conversion of 25-OH vitamin D to 1,25-(OH)₂ vitamin D by 1α-hydroxylase, which is activated by PTH 3. JG cells secrete renin in response to \downarrow renal arterial pressure and \uparrow renal sympathetic discharge (β_1 effect) 4. Secretion of prostaglandins that vasodilate the afferent arterioles to \uparrow GFR 	NSAIDs can cause acute renal failure in high vasoconstrictive states by inhibiting the renal production of prostaglandins, which keep the afferent arterioles vasodilated to maintain GFR.

Hormones acting on kidney



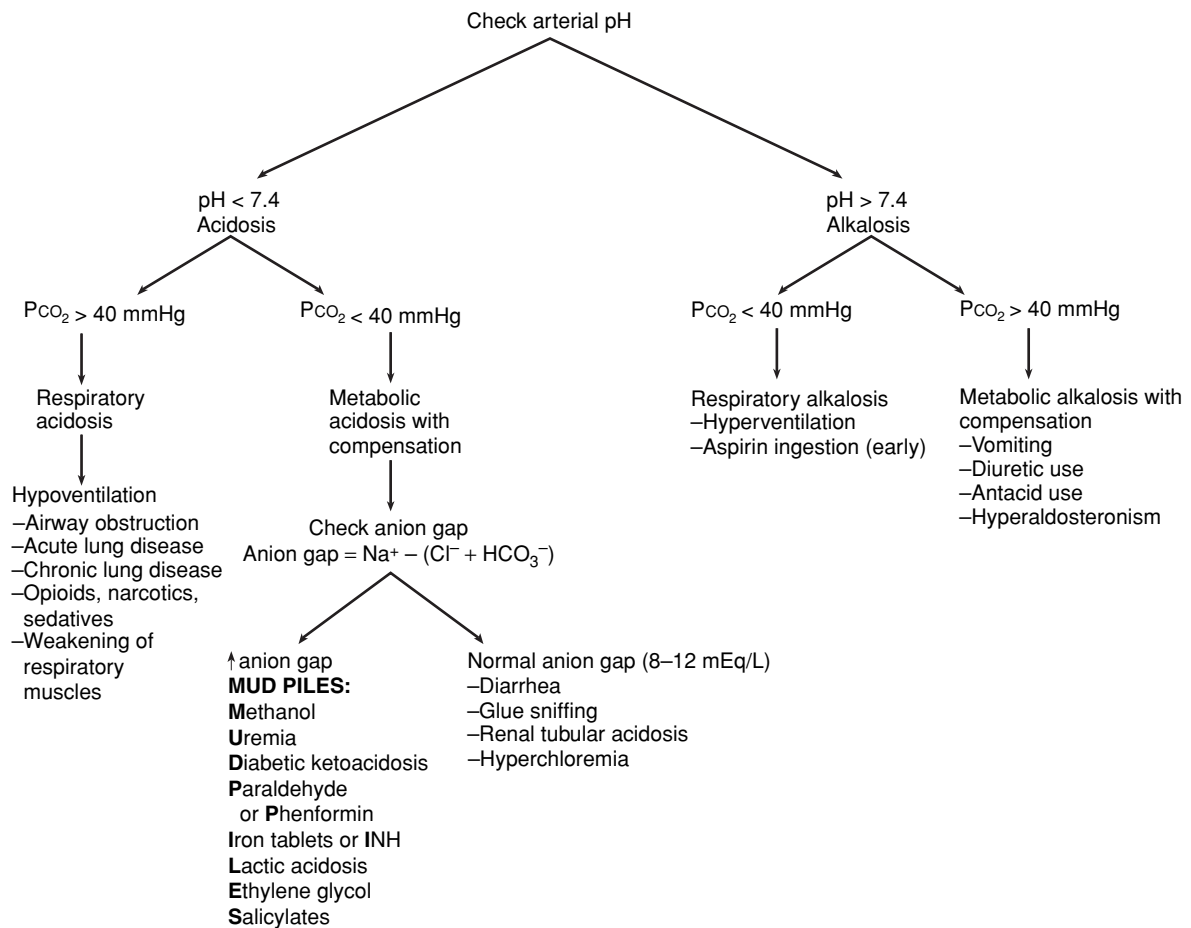
Acid-base physiology

	pH	Pco ₂	[HCO ₃ ⁻]	Compensatory response
Metabolic acidosis	↓	↓	↓	Hyperventilation
Metabolic alkalosis	↑	↑	↑	Hypoventilation
Respiratory acidosis	↓	↑	↑	Renal [HCO ₃ ⁻] reabsorption
Respiratory alkalosis	↑	↓	↓	Renal [HCO ₃ ⁻] secretion

$$\text{Henderson-Hasselbalch equation: } \text{pH} = \text{pKa} + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ Pco}_2}$$

Key: ↑ ↓ = primary disturbance; ↓ ↑ = compensatory response.

Acidosis/alkalosis



Acid-base compensations

Metabolic acidosis

Metabolic alkalosis

Respiratory acidosis

Respiratory alkalosis

The following formulas give appropriate compensations for a single disorder. If the formula does not match the actual values, suspect a mixed disorder.

Winter's formula: $\text{PCO}_2 = 1.5 (\text{HCO}_3^-) + 8 \pm 2$.

$\text{PCO}_2 \uparrow 0.7 \text{ mmHg}$ for every $\uparrow 1 \text{ mEq/L HCO}_3^-$.

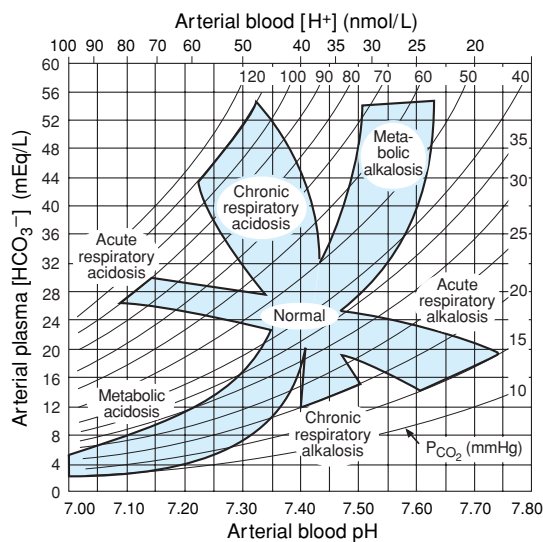
Acute— $\uparrow 1 \text{ mEq/L HCO}_3^-$ for every $\uparrow 10 \text{ mmHg PCO}_2$.

Chronic— $\uparrow 3.5 \text{ mEq/L HCO}_3^-$ for every $\uparrow 10 \text{ mmHg PCO}_2$.

Acute— $\downarrow 2 \text{ mEq/L HCO}_3^-$ for every $\downarrow 10 \text{ mmHg PCO}_2$.

Chronic— $\downarrow 5 \text{ mEq/L HCO}_3^-$ for every $\downarrow 10 \text{ mmHg PCO}_2$.

Acid-base nomogram



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

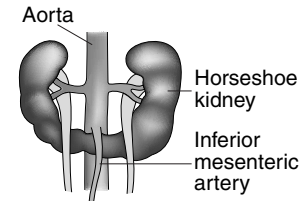
Potter's syndrome

Bilateral renal agenesis → oligohydramnios → limb deformities, facial deformities, pulmonary hypoplasia. Caused by malformation of ureteric bud.

Babies with Potter's can't "Pee" in utero.

Horseshoe kidney

Inferior poles of both kidneys fuse. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen.

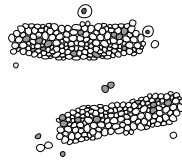


Casts

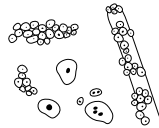
Casts in urine:

RBC casts—glomerular inflammation (nephritic syndromes), ischemia, or malignant hypertension.
WBC casts—tubulointerstitial disease, acute pyelonephritis, glomerular disorders.
Granular casts—acute tubular necrosis.
Waxy casts—advanced renal disease/CRF.
Hyaline casts—nonspecific.

Presence of casts indicates that hematuria/pyuria is of renal origin.
Bladder cancer → RBCs.
Acute cystitis → WBCs.



Red blood cell casts



White blood cell casts



Hyaline casts



Granular casts

Glomerular pathology

Nephritic syndrome —hematuria, hypertension, oliguria, azotemia.	I = inflammation.
1. Acute poststreptococcal glomerulonephritis — LM: glomeruli enlarged and hypercellular, neutrophils, “lumpy-bumpy.” EM: subepithelial humps. IF: granular pattern.	Most frequently seen in children. Peripheral and periorbital edema. Resolves spontaneously.
2. Rapidly progressive (crescentic) glomerulonephritis —LM and IF: crescent-moon shape.	Rapid course to renal failure from one of many causes.
3. Goodpasture’s syndrome (type II hypersensitivity) —IF: linear pattern, anti-GBM antibodies.	Hemoptysis, hematuria.
4. Membranoproliferative glomerulonephritis — EM: subendothelial humps, “tram track.”	Slowly progresses to renal failure.
5. IgA nephropathy (Berger’s disease) — IF and EM: mesangial deposits of IgA.	Mild disease. Often postinfectious.
6. Alport’s syndrome —split basement membrane.	Collagen IV mutation. Nerve deafness and ocular disorders.
Nephrotic syndrome —massive proteinuria, hypoalbuminemia, peripheral and periorbital edema, hyperlipidemia.	O = proteinuria.
1. Membranous glomerulonephritis —LM: diffuse capillary and basement membrane thickening. IF: granular pattern. EM: “spike and dome.”	A common cause of adult nephrotic syndrome.
2. Minimal change disease (lipoid nephrosis) — LM: normal glomeruli. EM: foot process effacement (see Color Image 93).	Most common cause of childhood nephrotic syndrome. Responds well to steroids.
3. Focal segmental glomerular sclerosis — LM: segmental sclerosis and hyalinosis.	More severe disease in HIV patients.
4. Diabetic nephropathy —LM: Kimmelstiel-Wilson “wire loop” lesions, basement membrane thickening (see Color Image 95).	
5. SLE (5 patterns of renal involvement)— LM: In membranous glomerulonephritis pattern, wire-loop lesion with subendothelial deposits.	

(LM = light microscopy; EM = electron microscopy; IF = immunofluorescence)

Kidney stones	Can lead to severe complications, such as hydronephrosis and pyelonephritis. 4 major types:	
Calcium	Most common kidney stones (75–85%). Calcium oxalate (see Color Image 97), calcium phosphate, or both. Conditions that cause hypercalcemia (cancer, ↑ PTH, ↑ vitamin D, milk-alkali syndrome) can lead to hypercalciuria and stones. Tend to recur.	Radiopaque.
Ammonium magnesium phosphate (struvite)	2nd most common kidney stone. Caused by infection with urease-positive bugs (<i>Proteus vulgaris</i> , <i>Staphylococcus</i> , <i>Klebsiella</i>). Can form staghorn calculi that can be a nidus for UTIs.	Radiopaque.
Uric acid	Strong association with hyperuricemia (e.g., gout). Often seen as a result of diseases with ↑ cell turnover, such as leukemia and myeloproliferative disorders.	Radiolucent.
Cystine	Most often 2° to cystinuria.	Radiolucent.
<hr/>		
Renal cell carcinoma	Most common renal malignancy. Most common in men ages 50–70. ↑ incidence with smoking and obesity. Associated with von Hippel–Lindau and gene deletion in chromosome 3. Originates in renal tubule cells → polygonal clear cells. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, and weight loss. Invades IVC and spreads hematogenously. Associated with paraneoplastic syndromes (ectopic EPO, ACTH, PTHrP, and prolactin) (see Color Image 98).	
<hr/>		
Wilms’ tumor	Most common renal malignancy of early childhood (ages 2–4). Presents with huge, palpable flank mass, hemihypertrophy. Deletion of tumor suppression gene <i>WT1</i> on chromosome 11. Can be part of WAGR complex: W ilms’ tumor, A niridia, G enitourinary malformation, and mental-motor R etardation.	
<hr/>		
Transitional cell carcinoma	Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder). Painless hematuria is suggestive of bladder cancer. Associated with problems in your Pee SAC : P henacetin, S moking, A niline dyes, and C yclophosphamide (see Color Image 90).	
<hr/>		
Pyelonephritis		
Acute	Affects cortex with relative sparing of glomeruli/vessels. White cell casts in urine are pathognomonic (see Color Image 89A). Presents with fever, CVA tenderness.	
Chronic	Coarse, asymmetric corticomedullary scarring. Tubules can contain eosinophilic casts (thyroidization of kidney) (see Color Image 89B).	
<hr/>		
Diffuse cortical necrosis	Acute generalized infarction of cortices of both kidneys. Likely due to a combination of vasospasm and DIC. Associated with obstetric catastrophes (e.g., abruptio placentae) and septic shock.	

Acute tubular necrosis Most common cause of acute renal failure. Reversible, but fatal if left untreated. Associated with renal ischemia (e.g., shock), crush injury (myoglobinuria), toxins. Death most often occurs during initial oliguric phase. Recovery in 2–3 weeks.

Renal papillary necrosis Associated with:

1. Diabetes mellitus
2. Acute pyelonephritis
3. Chronic phenacetin use

Acute renal failure Abrupt decline in renal function with \uparrow creatinine and \uparrow BUN over a period of several days.

1. Prerenal azotemia—decreased RBF (e.g., hypotension) \rightarrow \downarrow GFR. $\text{Na}^+/\text{H}_2\text{O}$ retained by kidney.
2. Intrinsic renal—generally due to acute tubular necrosis or ischemia/toxins. Patchy necrosis leads to debris obstructing tubule and fluid backflow across necrotic tubule \rightarrow \downarrow GFR. Urine has epithelial/granular casts.
3. Postrenal—outflow obstruction (stones, BPH, neoplasia). Develops only with bilateral obstruction.

Variable	Prerenal	Renal	Postrenal
Urine osmolality	> 500	< 350	< 350
Urine Na	< 10	> 20	> 40
Fe_{Na}	$< 1\%$	$> 2\%$	$> 4\%$
BUN/Cr ratio	> 20	< 15	> 15

Consequences of renal failure

Failure to make urine and excrete nitrogenous wastes.

Uremia—clinical syndrome marked by \uparrow BUN and \uparrow creatinine and associated symptoms.

Consequences:

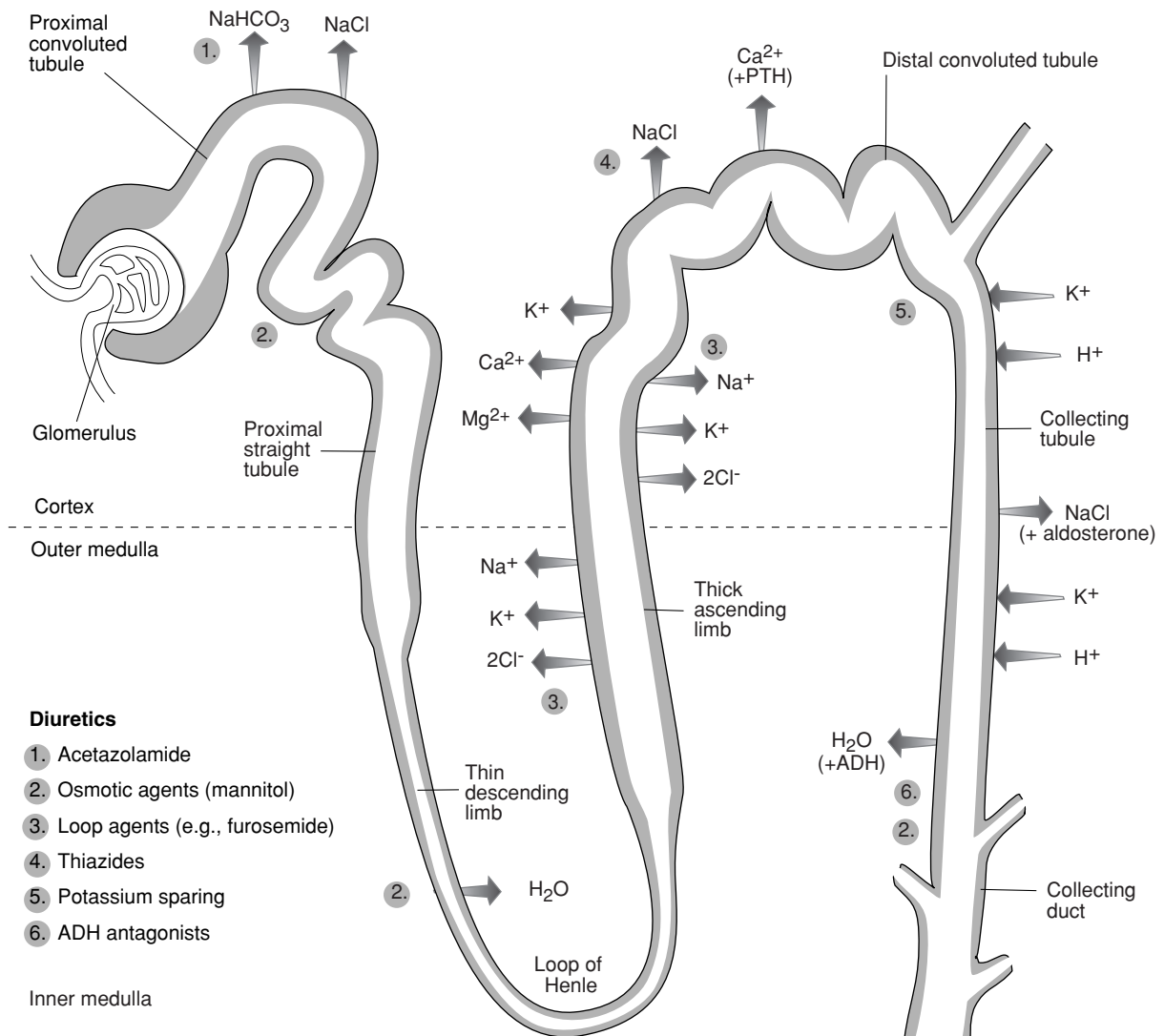
1. Anemia (failure of erythropoietin production)
2. Renal osteodystrophy (failure of active vitamin D production)
3. Hyperkalemia, which can lead to cardiac arrhythmias
4. Metabolic acidosis due to \downarrow acid secretion and \downarrow generation of HCO_3^-
5. Uremic encephalopathy
6. Sodium and H_2O excess \rightarrow CHF and pulmonary edema
7. Chronic pyelonephritis
8. Hypertension

2 forms of renal failure—acute renal failure (often due to hypoxia) and chronic renal failure (e.g., due to hypertension and diabetes).

Electrolyte disturbances

Electrolyte	Low serum concentration	High serum concentration
Na ⁺	Disorientation, stupor, coma	Neurologic: irritability, delirium, coma
Cl ⁻	2° to metabolic alkalosis	2° to non-anion gap acidosis
K ⁺	U waves on ECG, flattened T waves, arrhythmias, paralysis	Peaked T waves, arrhythmias
Ca ²⁺	Tetany, neuromuscular irritability	Delirium, renal stones, abdominal pain
Mg ²⁺	Neuromuscular irritability, arrhythmias	Delirium, ↓ DTRs, cardiopulmonary arrest
PO ₄ ²⁻	Low-mineral ion product causes bone loss	High-mineral ion product causes metastatic calcification, renal stones

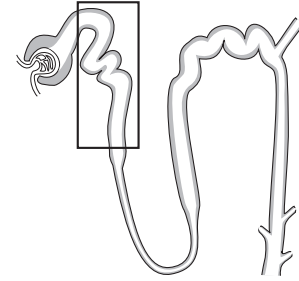
Diuretics: site of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:243.)

Mannitol

Mechanism	Osmotic diuretic, ↑ tubular fluid osmolarity, producing ↑ urine flow.
Clinical use	Shock, drug overdose, ↓ intracranial/intraocular pressure.
Toxicity	Pulmonary edema, dehydration. Contraindicated in anuria, CHF.



Acetazolamide

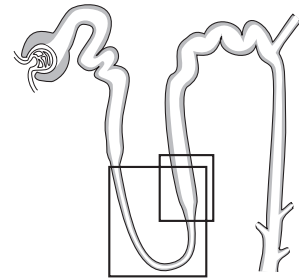
Mechanism	Carbonic anhydrase inhibitor. Causes self-limited NaHCO_3 diuresis and reduction in total-body HCO_3^- stores. Acts at the proximal convoluted tubule.
Clinical use	Glaucoma, urinary alkalization, metabolic alkalosis, altitude sickness.
Toxicity	Hyperchloremic metabolic acidosis, neuropathy, NH_3 toxicity, sulfa allergy.

ACIDazolamide causes **ACID**osis.

Furosemide

Mechanism	Sulfonamide loop diuretic. Inhibits cotransport system (Na^+ , K^+ , 2Cl^-) of thick ascending limb of loop of Henle. Abolishes hypertonicity of medulla, preventing concentration of urine. ↑ Ca^{2+} excretion. Loops Lose calcium.
Clinical use	Edematous states (CHF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
Toxicity	Ototoxicity, Hypokalemia, Dehydration, Allergy (sulfa), Nephritis (interstitial), Gout.

OH DANG!



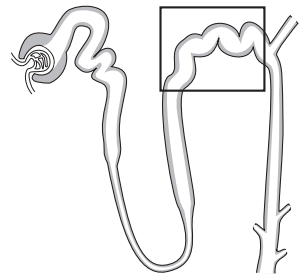
Ethacrynic acid

Mechanism	Phenoxyacetic acid derivative (NOT a sulfonamide). Essentially same action as furosemide.
Clinical use	Diuresis in patients allergic to sulfa drugs.
Toxicity	Similar to furosemide; can be used in hyperuricemia, acute gout (never used to treat gout).

Hydrochlorothiazide

Mechanism	Thiazide diuretic. Inhibits NaCl reabsorption in early distal tubule, reducing diluting capacity of the nephron. ↓ Ca^{2+} excretion.
Clinical use	Hypertension, CHF, idiopathic hypercalciuria, nephrogenic diabetes insipidus.
Toxicity	Hypokalemic metabolic alkalosis, hyponatremia, hyperGlycemia, hyperLipidemia, hyperUricemia, and hyperCalcemia. Sulfa allergy.

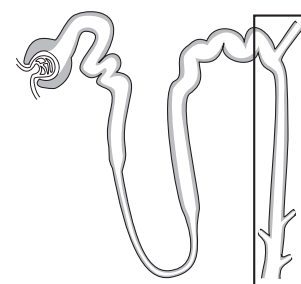
HyperGLUC.



K⁺-sparing diuretics

Mechanism

Spironolactone, Triamterene, Amiloride, eplerenone.
Spironolactone is a competitive aldosterone receptor antagonist in the cortical collecting tubule.

The K⁺ STAYS.

Clinical use

Triamterene and amiloride act at the same part of the tubule by blocking Na⁺ channels in the CCT.

Toxicity

Hyperaldosteronism, K⁺ depletion, CHF.
Hyperkalemia, endocrine effects (e.g., spironolactone causes gynecomastia, antiandrogen effects).

Diuretics: electrolyte changes

Urine NaCl

↑ (all diuretics—carbonic anhydrase inhibitors, loop diuretics, thiazides, K⁺-sparing diuretics).

Urine K⁺

↑ (all except K⁺-sparing diuretics).

Blood pH

↓ (acidosis)—carbonic anhydrase inhibitors, K⁺-sparing diuretics; ↑ (alkalosis)—loop diuretics, thiazides.

Urine Ca⁺

↑ loop diuretics, ↓ thiazides.

ACE inhibitors

Mechanism

Captopril, enalapril, lisinopril.
Inhibit angiotensin-converting enzyme, reducing levels of angiotensin II and preventing inactivation of bradykinin, a potent vasodilator.
Renin release is ↑ due to loss of feedback inhibition.

Losartan is an angiotensin II receptor antagonist. It is **not** an ACE inhibitor and does not cause cough.

Clinical use

Hypertension, CHF, diabetic renal disease.

Toxicity

Cough, Angioedema, Proteinuria, Taste changes, hypOtension, Pregnancy problems (fetal renal damage), Rash, Increased renin, Lower angiotensin II. Also hyperkalemia.

CAPTOPRIL.

[illegible]

Reproductive

“Artificial insemination is when the farmer does it to the cow instead of the bull.”

—Student essay

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

► REPRODUCTIVE—HIGH-YIELD CLINICAL VIGNETTES

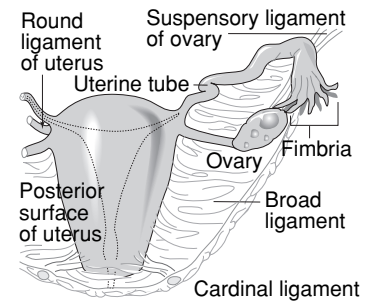
- | | | |
|---|---|--|
| ■ 24-year-old male develops testicular cancer. | Metastatic spread occurs by what route? | Para-aortic lymph nodes (recall descent of testes during development). |
| ■ Woman with previous cesarean section has a scar in her lower uterus close to the opening of the os. | What is she at ↑ risk for? | Placenta previa. |
| ■ Obese woman presents with hirsutism and ↑ levels of serum testosterone. | What is the diagnosis? | Polycystic ovarian syndrome. |
| ■ Pregnant woman at 16 weeks of gestation presents with an atypically large abdomen. | What is the diagnosis? | High hCG; hydatidiform mole. |
| ■ 55-year-old postmenopausal woman is on tamoxifen therapy. | What is she at ↑ risk of acquiring? | Endometrial carcinoma. |

Gonadal venous drainage

Left ovary/testis → left gonadal vein → left renal vein → IVC.
Right ovary/testis → right gonadal vein → IVC.

Ligaments of the uterus

Suspensory ligament of ovaries	Contains the ovarian vessels.
Transverse cervical (cardinal) ligament	Contains the uterine vessels.
Round ligament of uterus	Contains no important structures.
Broad ligament	Contains the round ligaments of the uterus and ovaries and the uterine tubules and vessels.



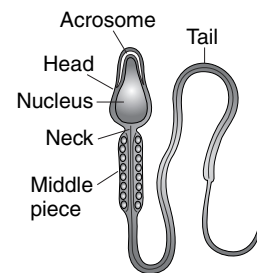
Autonomic innervation of the male sexual response

Erection is mediated by the Parasympathetic nervous system.
Emission is mediated by the Sympathetic nervous system.
Ejaculation is mediated by visceral and somatic nerves.

Point and Shoot.

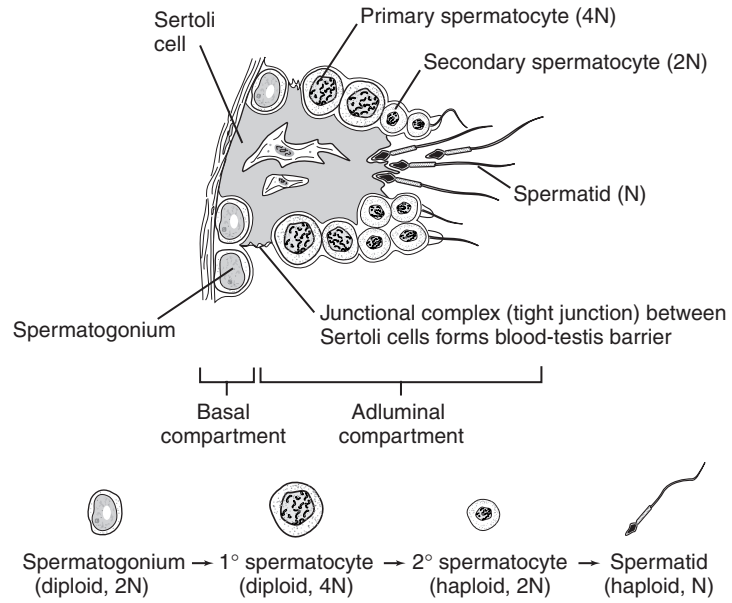
Derivation of sperm parts

Acrosome is derived from the Golgi apparatus and flagellum (tail) from one of the centrioles. Middle piece (neck) has Mitochondria. Sperm food supply is fructose.

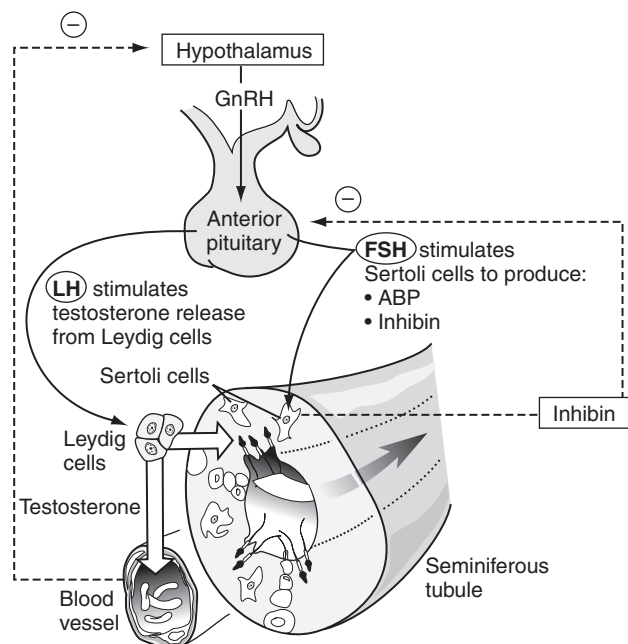


**Sperm
development**

Spermatogenesis begins with spermatogonia (type A and type B). Full development takes 2 months. Spermatogenesis occurs in Seminiferous tubules. Type A forms both type A and type B spermatogonia.



Male spermatogenesis



PRODUCTS	FUNCTIONS OF PRODUCTS
Androgen-binding protein (ABP)	Ensures that testosterone in seminiferous tubule is high
Inhibin	Inhibits FSH
Testosterone	Differentiates male genitalia, has anabolic effects on protein metabolism, maintains gametogenesis, maintains libido, inhibits GnRH, and fuses epiphyseal plates in bone.

FSH → Sertoli cells → Sperm production
 LH → Leydig cell

Androgens

Source

Testosterone, dihydrotestosterone (DHT), and androstenedione.

Source

DHT and testosterone (testis), androstenedione (adrenal).

Potency—DHT > testosterone > androstenedione.

Targets

Skin, prostate, seminal vesicles, epididymis, liver, muscle, brain.

Testosterone is converted to DHT by the enzyme 5 α -reductase, which is inhibited by finasteride.

Function

1. Differentiation of wolffian duct system into internal gonadal structures
2. 2° sexual characteristics and growth spurt during puberty
3. Required for normal spermatogenesis
4. Anabolic effects— \uparrow muscle size, \uparrow RBC production
5. \uparrow libido

Testosterone and androstenedione are converted to estrogen in adipose tissue by enzyme aromatase.

Estrogen

Source

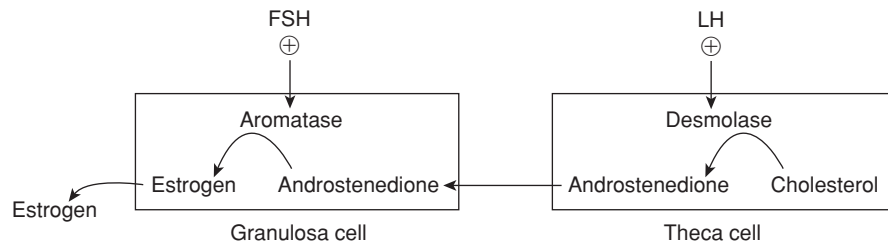
Ovary (estradiol), placenta (estriol), blood (aromatization).

Potency—estradiol > estrone > estriol.

Function

1. Growth of follicle
2. Endometrial proliferation, myometrial excitability
3. Development of genitalia
4. Stromal development of breast
5. Female fat distribution
6. Hepatic synthesis of transport proteins
7. Feedback inhibition of FSH
8. LH surge (estrogen feedback on LH secretion switches to positive from negative just before LH surge)
9. ↑ myometrial excitability
10. ↑ HDL, ↓ LDL

Estrogen hormone replacement therapy after menopause →
↓ hot flashes and
↓ postmenopausal bone loss.
Unopposed estrogen therapy—
↑ risk of endometrial cancer;
use of progesterone with
estrogen ↓ this risk.



Progesterone

Source

Corpus luteum, placenta, adrenal cortex, testes.

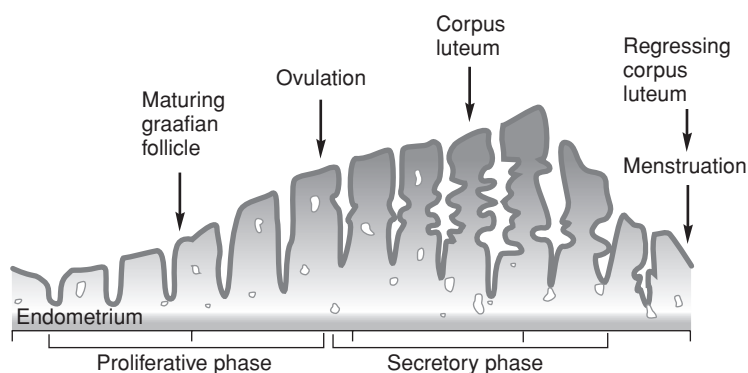
Elevation of progesterone is indicative of ovulation.

Function

1. Stimulation of endometrial glandular secretions and spiral artery development
2. Maintenance of pregnancy
3. ↓ myometrial excitability
4. Production of thick cervical mucus, which inhibits sperm entry into the uterus
5. ↑ body temperature
6. Inhibition of gonadotropins (LH, FSH)
7. Uterine smooth muscle relaxation

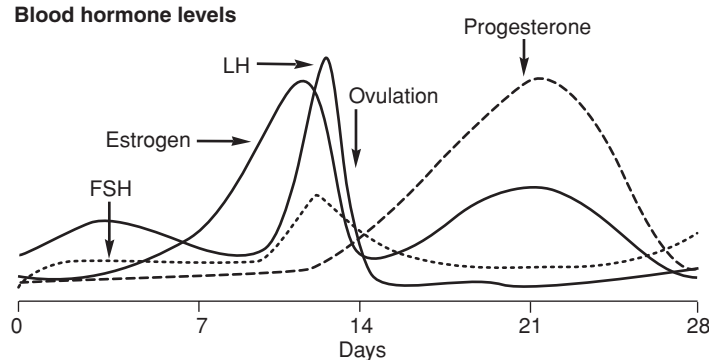
Progesterone Prepares for Pregnancy.

Menstrual cycle



Follicular growth is fastest during 2nd week of proliferative phase.
 Estrogen stimulates endometrial proliferation.
 Progesterone maintains endometrium to support implantation.
 \downarrow progesterone leads to \downarrow fertility.

Blood hormone levels



Ovulation

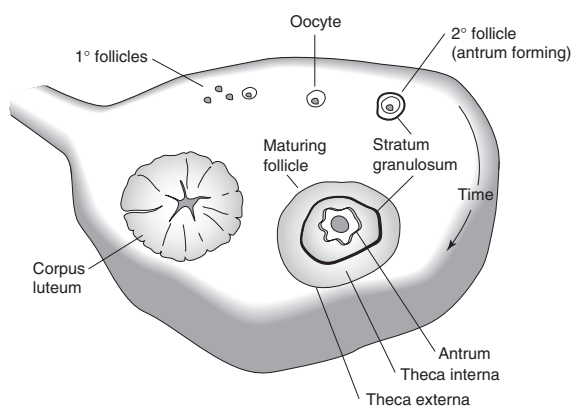
Estrogen surge day before ovulation.
 Stimulates LH, inhibits FSH.
 LH surge causes ovulation (rupture of follicle).
 \uparrow temperature (progesterone induced).
 Ferning of cervical mucosa.
 Oral contraceptives prevent estrogen surge, LH surge \rightarrow ovulation does not occur.

Mittelschmerz—blood from ruptured follicle causes peritoneal irritation that can mimic appendicitis.

Meiosis and ovulation

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.
 Meiosis I is arrested in proPhase for years until Ovulation.
 Meiosis II is arrested in METaphase until fertilization.

An egg MET a sperm.



hCG

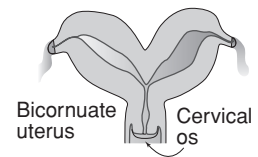
Source	Syncytiotrophoblast of placenta.
Function	<ol style="list-style-type: none"> 1. Maintains the corpus luteum for the 1st trimester by acting like LH. In the 2nd and 3rd trimester, the placenta synthesizes its own estrogen and progesterone and the corpus luteum degenerates. 2. Used to detect pregnancy because it appears in the urine 8 days after successful fertilization (blood and urine tests available). 3. Elevated hCG in women with hydatidiform moles or choriocarcinoma.

Menopause

Cessation of estrogen production with age-linked decline in number of ovarian follicles. Average age of onset is 51 years (earlier in smokers).	<p>Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.</p> <p>Menopause causes HAVOC: Hot flashes, Atrophy of the Vagina, Osteoporosis, Coronary artery disease.</p>
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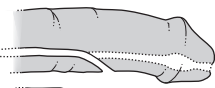
Bicornuate uterus

Results from incomplete fusion of the paramesonephric ducts. Associated with urinary tract abnormalities and infertility.



Congenital penile abnormalities

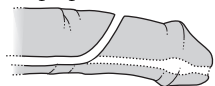
Hypospadias



Abnormal opening of penile urethra on inferior (ventral) side of penis due to failure of urethral folds to close.

Hypospadias is more common than epispadias. Fix hypospadias to prevent UTIs.

Epispadias



Abnormal opening of penile urethra on superior (dorsal) side of penis due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with epispadias.

Sex chromosome disorders

Klinefelter's syndrome
[male] (XXY),
1:850

Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution. Presence of inactivated X chromosome (Barr body). (see Image 107).

Common cause of hypogonadism seen in infertility workup.

Turner's syndrome
[female] (XO),
1:3000

Short stature, ovarian dysgenesis (streak ovary), webbing of neck, coarctation of the aorta, most common cause of 1° amenorrhea. No Barr body. (see Image 108).

“Hugs and kisses” (XO) from Tina Turner (female).

Double Y males
[male] (XYY),
1:1000

Phenotypically normal, very tall, severe acne, antisocial behavior (seen in 1–2% of XYY males).

Observed with ↑ frequency among inmates of penal institutions.

Pseudohermaphroditism

Disagreement between the phenotypic (external genitalia) and gonadal (testes vs. ovaries) sex.

Female pseudohermaphrodite
(XX)

Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (i.e., congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

Male pseudohermaphrodite
(XY)

Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

True hermaphrodite
(46,XX or 47,XXY)

Both ovary and testicular tissue present; ambiguous genitalia. Very rare.

Androgen insensitivity syndrome (46,XY)

Defect in androgen receptor resulting in normal-appearing female; female external genitalia with rudimentary vagina; uterus and uterine tubes generally absent; develops testes (often found in labia majora; surgically removed to prevent malignancy). Levels of testosterone, estrogen, and LH are all high.

5α-reductase deficiency	Unable to convert testosterone to DHT. Ambiguous genitalia until puberty, when \uparrow testosterone causes masculinization of genitalia. Testosterone/estrogen levels are normal; LH is normal or \uparrow .
Benign prostatic hyperplasia	Common in men > 50 years of age. May be due to an age-related increase in estradiol with possible sensitization of the prostate to the growth-promoting effects of DHT. Characterized by a nodular enlargement of the periurethral (lateral and middle) lobes of the prostate gland, compressing the urethra into a vertical slit. Often presents with \uparrow frequency of urination, nocturia, difficulty starting and stopping the stream of urine, and dysuria. May lead to distention and hypertrophy of the bladder, hydronephrosis, and UTIs. Not considered a premalignant lesion.
Prostatic adenocarcinoma	Common in men > 50 years of age. Arises most often from the posterior lobe (peripheral zone) of the prostate gland and is most frequently diagnosed by digital rectal examination (hard nodule) and prostate biopsy. Prostatic acid phosphatase and prostate-specific antigen (PSA) are useful tumor markers. Osteoblastic metastases in bone may develop in late stages, as indicated by an \uparrow in serum alkaline phosphatase and PSA.
Hydatidiform mole	A pathologic ovum (“empty egg”—ovum with no DNA) resulting in cystic swelling of chorionic villi and proliferation of chorionic epithelium (trophoblast). Most common precursor of choriocarcinoma. High β -hCG. “Honeycombed uterus,” “cluster of grapes” appearance. Genotype of a complete mole is 46,XX and is completely paternal in origin (no maternal chromosomes); no associated fetus. PART ial mole is made up of 3 or more PARTS (triploid or tetraploid); may contain fetal PARTS (see Color Image 74).
Pregnancy-induced hypertension (preeclampsia-eclampsia)	Preeclampsia is the triad of hypertension, proteinuria, and edema; eclampsia is the addition of seizures to the triad. Affects 7% of pregnant women from 20 weeks’ gestation to 6 weeks postpartum. \uparrow incidence in patients with preexisting hypertension, diabetes, chronic renal disease, and autoimmune disorders. Etiology involves placental ischemia. Can be associated with HELLP syndrome (H emolysis, E levated LFTs , L ow P latelets).
Clinical features	Headache, blurred vision, abdominal pain, edema of face and extremities, altered mentation, hyperreflexia; lab findings may include thrombocytopenia, hyperuricemia.
Treatment	Delivery of fetus as soon as viable. Otherwise bed rest, salt restriction, and monitoring and treatment of hypertension. For eclampsia, a medical emergency, IV magnesium sulfate and diazepam.
Pregnancy complications	<ol style="list-style-type: none"> 1. Abruptio placentae—premature separation of placenta. Painful uterine bleeding (usually during 3rd trimester). Fetal death. May be associated with DIC. \uparrow risk with smoking, hypertension, cocaine use. 2. Placenta accreta—defective decidual layer allows placenta to attach directly to myometrium. Predisposed by prior C-section or inflammation. May have massive hemorrhage after delivery. 3. Placenta previa—attachment of placenta to lower uterine segment. May occlude cervical os. Painless bleeding in any trimester. 4. Ectopic pregnancy—most often in fallopian tubes, predisposed by salpingitis (PID). Suspect with \uparrow hCG and sudden lower abdominal pain; confirm with ultrasound.

Amniotic fluid abnormalities

Polyhydramnios	> 1.5–2 L of amniotic fluid; associated with esophageal/duodenal atresia, causing inability to swallow amniotic fluid, and with anencephaly.
Oligohydramnios	< 0.5 L of amniotic fluid; associated with bilateral renal agenesis or posterior urethral valves (in males) and resultant inability to excrete urine.

Cervical pathology

Dysplasia and carcinoma in situ	Disordered epithelial growth; begins at basal layer and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (carcinoma in situ), depending on extent of dysplasia. Associated with HPV 16, 18. May progress slowly to invasive carcinoma.
Invasive carcinoma	Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Lateral invasion can block ureters, causing renal failure.

Uterine pathology

Endometriosis	Non-neoplastic endometrial glands/stroma in abnormal locations outside the uterus. Characterized by cyclic bleeding (menstrual type) from ectopic endometrial tissue resulting in blood-filled “chocolate cysts.” In ovary or on peritoneum. Manifests clinically as severe menstrual-related pain. Often results in infertility (see Color Image 77).
Adenomyosis	Endometriosis within the myometrium.
Endometrial hyperplasia	Abnormal endometrial gland proliferation usually caused by excess estrogen stimulation. ↑ risk for endometrial carcinoma. Most commonly manifests clinically as vaginal bleeding.
Endometrial carcinoma	Most common gynecologic malignancy. Peak age 55–65 years old. Clinically presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged estrogen use (compare with carcinomas of cervix), obesity, diabetes, and hypertension.
Leiomyoma	Most common of all tumors in females. Often presents with multiple tumors. ↑ incidence in blacks. Malignant transformation is rare. Estrogen sensitive—tumor size ↑ with pregnancy and ↓ with menopause. Does not progress to leiomyosarcoma (see Image 122).
Leiomyosarcoma	Bulky tumor with areas of necrosis and hemorrhage, typically arising de novo (not from leiomyoma). ↑ incidence in blacks. Highly aggressive tumor with tendency to recur. May protrude from cervix and bleed.

Polycystic ovarian syndrome

↑ LH production leads to anovulation, hyperandrogenism due to deranged steroid synthesis. Manifest clinically by amenorrhea, infertility, obesity, and hirsutism. Treat with weight loss, OCPs, gonadotropin analogs, or surgery.

Ovarian cysts

1. Follicular cyst—distention of unruptured graafian follicle. May be associated with hyperestrinism and endometrial hyperplasia.
2. Corpus luteum cyst—hemorrhage into persistent corpus luteum. Menstrual irregularity.
3. Theca-lutein cyst—often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and moles.
4. “Chocolate cyst”—blood-containing cyst from ovarian endometriosis. Varies with menstrual cycle.

Germ cell tumors

Germinomas	Most common malignant germ cell tumor of the ovaries (dysgerminoma) and testes (seminoma). Sheets of uniform cells, ↑ hCG. Seminoma presents with painless testicular enlargement; ↑ risk with cryptorchidism.
Yolk sac (endodermal sinus) tumor	Aggressive malignancy in ovaries, testes, sacrococcygeal area of young children. Schiller-Duval bodies, primitive glomeruli. ↑ AFP.
Choriocarcinoma	Rare but malignant; can develop during pregnancy in mother or baby. Large, hyperchromatic syncytiotrophoblastic cells. ↑ hCG.
Embryonal carcinoma	2nd most common testicular germ cell tumor; painful mass. Glandular with papillary convolutions.
Teratoma	90% of ovarian germ cell tumors. Contain cells from 3 germ layers. In females, mature teratoma (“dermoid cyst”) is benign, while immature form is aggressively malignant. In Men, Mature teratomas are Malignant and painful; can present with gynecomastia. Struma ovarii—contains functional thyroid tissue (see Images 123, 124).

Ovarian non-germ cell tumors

1. Serous cystadenoma—20% of ovarian tumors. Frequently bilateral, lined with fallopian tube-like epithelium. Benign.
2. Serous cystadenocarcinoma—50% ovarian tumors, malignant and frequently bilateral.
3. Mucinous cystadenoma—multilocular cyst lined by mucus-secreting epithelium. Benign.
4. Mucinous cystadenocarcinoma—malignant. Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.
5. Brenner tumor—benign tumor that resembles Bladder epithelium.
6. Ovarian fibroma—bundles of spindle-shaped fibroblasts. Meigs’ syndrome—triad of ovarian fibroma, ascites, and hydrothorax.
7. Granulosa cell tumor—secretes estrogen → precocious puberty (kids). Can cause endometrial hyperplasia or carcinoma in adults. Call-Exner bodies—small follicles filled with eosinophilic secretions.

Testicular non-germ cell tumors

Leydig cell	Benign, contains Reinke crystals; androgen producing → gynecomastia in men, precocious puberty in boys.
Sertoli cell	Benign, androblastoma from sex cord stroma.
Testicular lymphoma	Most common testicular cancer in older men.

Breast disease

Type	Characteristics
Fibrocystic disease	<p>Presents with diffuse breast pain and multiple lesions, often bilateral. Biopsy shows fibrocystic elements. Usually does not indicate ↑ risk of carcinoma. Histologic types:</p> <ol style="list-style-type: none"> 1. Fibrosis—hyperplasia of breast stroma. 2. Cystic—fluid filled. 3. Sclerosing—↑ acini and intralobular fibrosis. 4. Epithelial hyperplasia—↑ in number of epithelial cell layers in terminal duct lobule. ↑ risk of carcinoma with atypical cells. Occurs > 30 years.
Benign tumors	<p>Fibroadenoma—most common tumor < 25 years. Small, mobile, firm mass with sharp edges. ↑ size and tenderness with pregnancy. Not a precursor to breast cancer.</p> <p>Cystosarcoma phyllodes—large, bulky mass of connective tissue and cysts. Tumor may have “leaflike” projections.</p> <p>Intraductal papilloma—tumor of lactiferous ducts; presents with nipple discharge.</p>
Malignant tumors (carcinoma)	<p>Common postmenopause. Arise from mammary duct epithelium or lobular glands.</p> <p>Overexpression of estrogen/progesterone receptors or <i>erb</i>-B2 (HER-2, an EGF receptor) is common; affects therapy and prognosis.</p> <p>Histologic types:</p> <ol style="list-style-type: none"> 1. Ductal carcinoma in situ (DCIS)—early malignancy without basement membrane penetration. 2. Invasive ductal, no specific type—firm, fibrous mass. Common. 3. Comedocarcinoma—ductal, with cheesy consistency due to central necrosis. 4. Inflammatory—lymphatic involvement; poor prognosis. 5. Invasive lobular—often multiple, bilateral. 6. Medullary—fleshy, cellular, lymphocytic infiltrate. Good prognosis. 7. Paget’s disease of the breast—eczematous patches on nipple. Paget cells—large cells with clear halo; suggest underlying carcinoma. Also seen on vulva.
Risk factors	<p>Gender, age, early 1st menarche (< 12 years old), delayed 1st pregnancy (> 30 years old), late menopause (> 50 years old), family history of 1st-degree relative with breast cancer at a young age. Risk is NOT increased by fibroadenoma or nonhyperplastic cysts.</p>

Antiandrogens

Finasteride	A 5 α -reductase inhibitor (\downarrow conversion of testosterone to dihydrotestosterone). Useful in BPH. Also promotes hair growth—used to treat male-pattern baldness.
Flutamide	A nonsteroidal competitive inhibitor of androgens at the testosterone receptor. Used in prostate carcinoma.
Ketoconazole, spironolactone	Inhibit steroid synthesis; used in the treatment of polycystic ovarian syndrome to prevent hirsutism.

Sildenafil, vardenafil

Mechanism	Inhibit cGMP phosphodiesterase, causing \uparrow cGMP, smooth muscle relaxation in the corpus cavernosum, \uparrow blood flow, and penile erection.	Sildenafil and vardenafil fill the penis.
Clinical use	Treatment of erectile dysfunction.	
Toxicity	Headache, flushing, dyspepsia, blue-green color vision. Risk of life-threatening hypotension in patients taking nitrates.	

Leuprolide

Mechanism	GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion.	When used in continuous fashion, it causes a transient initial burst of LH and FSH.
Clinical use	Infertility (pulsatile), prostate cancer (continuous—use with flutamide), uterine fibroids.	
Toxicity	Antiandrogen, nausea, vomiting.	

Clomiphene

Mechanism	A partial agonist at estrogen receptors in the pituitary gland. Prevents normal feedback inhibition and \uparrow release of LH and FSH from the pituitary, which stimulates ovulation.
Clinical use	Treatment of infertility.
Toxicity	Hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.

Mifepristone (RU-486)

Mechanism	Competitive inhibitor of progestins at progesterone receptors.
Clinical use	Abortifacient (prevents implantation).
Toxicity	Heavy bleeding, GI effects (nausea, vomiting, anorexia), abdominal pain.

Oral contraception (synthetic progestins, estrogen)

Advantages	Disadvantages
Reliable (< 1% failure)	Taken daily
\downarrow risk of endometrial and ovarian cancer	No protection against STDs
\downarrow incidence of ectopic pregnancy	\uparrow triglycerides
\downarrow pelvic infections	Depression, weight gain, nausea, hypertension
Regulation of menses	Hypercoagulable state

Respiratory

“There’s so much pollution in the air now that if it weren’t for our lungs, there’d be no place to put it all.”

—Robert Orben

“Mars is essentially in the same orbit. Somewhat the same distance from the Sun, which is very important. We have seen pictures where there are canals, we believe, and water. If there is water, that means there is oxygen. If there is oxygen, that means we can breathe.”

—Former Vice President Dan Quayle

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

► RESPIRATORY—HIGH-YIELD CLINICAL VIGNETTES

- | | | |
|--|-------------------------------------|---------------------------|
| ■ Patient exhibits an extended expiratory phase. | What is the disease process? | Obstructive lung disease. |
| ■ Tall, thin male teenager has abrupt-onset dyspnea and left-sided chest pain. There is hyperresonant percussion on the affected side, and breath sounds are diminished. | What is the diagnosis? | Spontaneous pneumothorax. |
| ■ Young man is concerned about his wife's inability to conceive and her recurrent URIs. She has dextrocardia. | Which of her proteins is defective? | Dynein (Kartagener's). |

Pneumocytes

Pseudocolumnar ciliated cells extend to the respiratory bronchioles; goblet cells extend only to the terminal bronchioles.

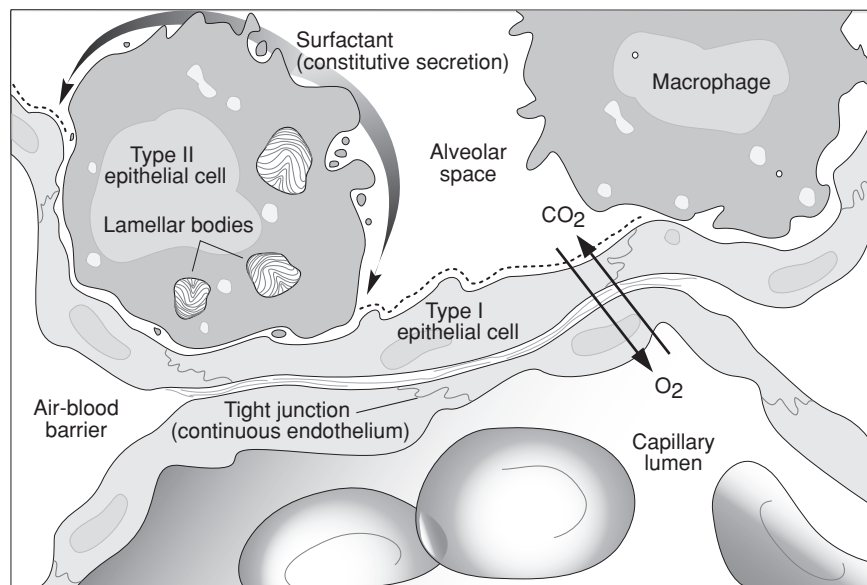
Type I cells (97% of alveolar surfaces) line the alveoli.

Type II cells (3%) secrete pulmonary surfactant (dipalmitoyl phosphatidylcholine), which ↓ the alveolar surface tension. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.

Mucus secretions are swept out of the lungs toward the mouth by ciliated cells.

A lecithin-to-sphingomyelin ratio of > 2.0 in amniotic fluid is indicative of fetal lung maturity.

Gas exchange barrier



Bronchopulmonary segments

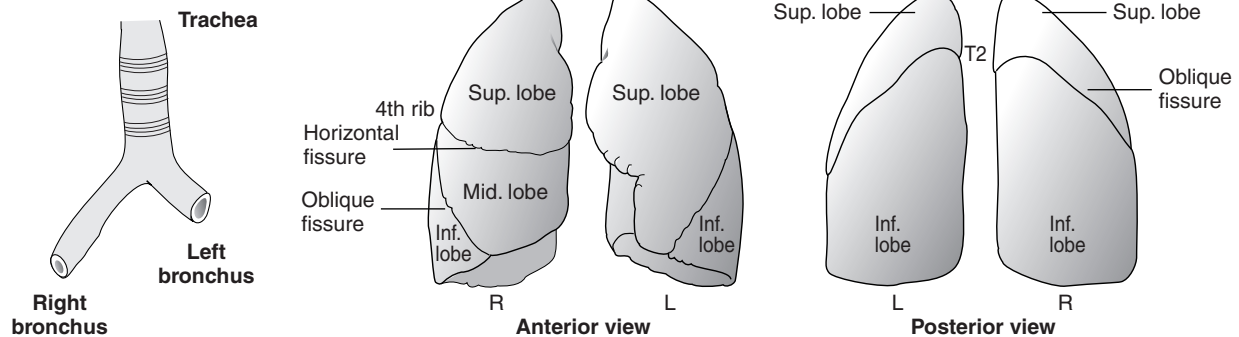
Each bronchopulmonary segment has a 3° (segmental) bronchus and 2 arteries (bronchial and pulmonary) in the center; veins and lymphatics drain along the borders.

Arteries run with Airways.

Lung relations

Right lung has 3 lobes; Left has 2 lobes and Lingula (homologue of right middle lobe). Right lung is more common site for inhaled foreign body owing to less acute angle of right main stem bronchus.

Instead of a middle lobe, the left lung has a space occupied by the heart. The relation of the pulmonary artery to the bronchus at each lung hilus is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior.



Diaphragm structures

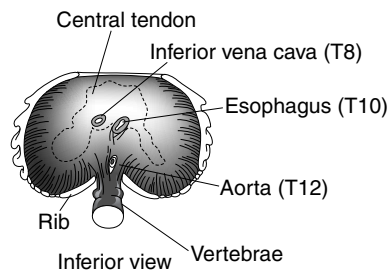
Structures perforating diaphragm:

At T8: IVC.

At T10: esophagus, vagus (2 trunks).

At T12: aorta (red), thoracic duct (white), azygous vein (blue).

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from the diaphragm can be referred to the shoulder.



I 8 10 EGGs AT 12:

I = IVC @ 8th vertebra; **EG** = Esophagus; **G** = vagus @ 10th vertebra; **A** = Aorta, Azygous; **T** = Thoracic duct @ 12th vertebra.

“C3, 4, 5 keeps the diaphragm alive.”

Muscles of respiration

Quiet breathing:

Inspiration—diaphragm.

Expiration—passive.

Exercise:

Inspiration—external intercostals, scalene muscles, sternomastoids.

Expiration—rectus abdominis, internal and external obliques, transversus abdominis, internal intercostals.

Response to high altitude

1. Acute ↑ in ventilation
2. Chronic ↑ in ventilation
3. ↑ erythropoietin → ↑ hematocrit and hemoglobin (chronic hypoxia)
4. ↑ 2,3-DPG (binds to hemoglobin so that hemoglobin releases more O₂)
5. Cellular changes (↑ mitochondria)
6. ↑ renal excretion of bicarbonate (e.g., can augment by use of acetazolamide) to compensate for the respiratory alkalosis
7. Chronic hypoxic pulmonary vasoconstriction results in RVH

Important lung products

1. Surfactant—produced by type II pneumocytes, ↓ alveolar surface tension, ↑ compliance
2. Prostaglandins
3. Histamine
4. Angiotensin-converting enzyme (ACE)—angiotensin I → angiotensin II; inactivates bradykinin (ACE inhibitors ↑ bradykinin and cause cough, angioedema)
5. Kallikrein—activates bradykinin

Surfactant—dipalmitoyl phosphatidylcholine (lecithin) deficient in neonatal RDS.

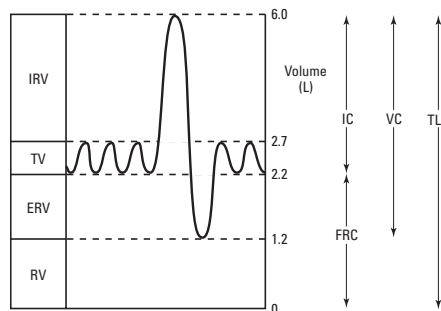
$$\text{Collapsing pressure} = \frac{2 (\text{tension})}{\text{radius}}$$

Lung volumes

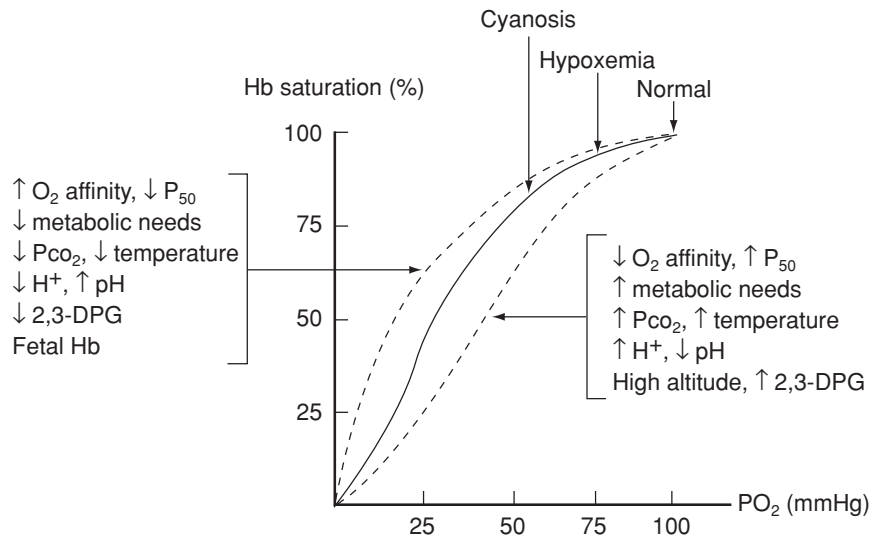
1. Residual volume (RV)—air in lung after maximal expiration
2. Expiratory reserve volume (ERV)—air that can still be breathed out after normal expiration
3. Tidal volume (TV)—air that moves into lung with each quiet inspiration, typically 500 mL
4. Inspiratory reserve volume (IRV)—air in excess of tidal volume that moves into lung on maximum inspiration
5. Vital capacity (VC)—TV + IRV + ERV
6. Functional reserve capacity (FRC)—RV + ERV (volume in lungs after normal expiration)
7. Inspiratory capacity (IC)—IRV + TV
8. Total lung capacity—TLC = IRV + TV + ERV + RV

Vital capacity is everything but the residual volume.

A capacity is a sum of ≥ 2 volumes.



Oxygen-hemoglobin dissociation curve



When curve shifts to the right,
↓ affinity of hemoglobin
for O₂ (facilitates unloading
of O₂ to tissue).

An ↑ in all factors (except pH)
causes a shift of the curve
to the right.

A ↓ in all factors (except pH)
causes a shift of the curve to
the left.

Right shift—CADET face right:

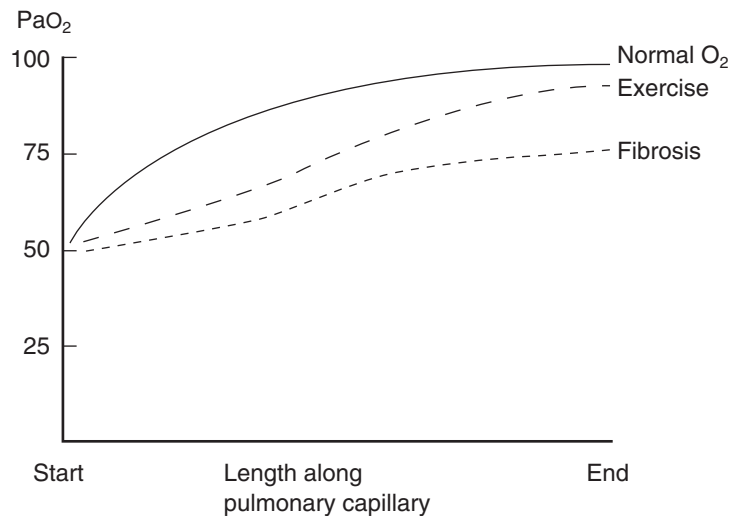
CO₂
Acid/Altitude
DPG (2,3-DPG)
Exercise
Temperature

Pulmonary circulation

Normally a low-resistance, high-compliance system. PO₂ and PCO₂ exert opposite effects on pulmonary and systemic circulation. A ↓ in PaO₂ causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

1. Perfusion limited—O₂ (normal health), CO₂, N₂O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.
2. Diffusion limited—O₂ (exercise, emphysema, fibrosis), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure (jugular venous distention, edema, hepatomegaly).

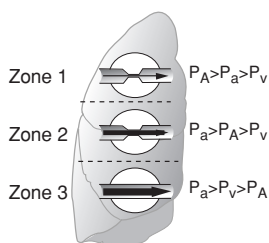


Determination of physiologic dead space

$$V_D = V_T \times \frac{(P_a\text{CO}_2 - P_e\text{CO}_2)}{P_a\text{CO}_2}$$

$P_a\text{CO}_2$ = arterial $P\text{CO}_2$, $P_e\text{CO}_2$ = expired air $P\text{CO}_2$.

V/Q mismatch



Ideally, ventilation is matched to perfusion (i.e., $V/Q = 1$) in order for adequate gas exchange.

Lung zones:

1. Apex of the lung— $V/Q = 3$ (wasted ventilation)
2. Base of the lung— $V/Q = 0.6$ (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (\uparrow cardiac output), there is vasodilation of apical capillaries, resulting in a V/Q ratio that approaches 1.

Certain organisms that thrive in high O_2 (e.g., TB) flourish in the apex.

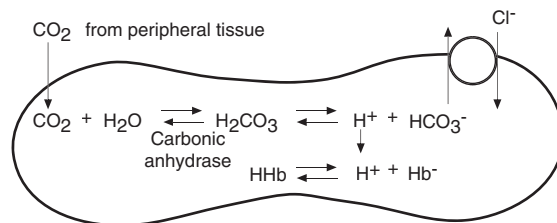
$V/Q \rightarrow 0$ = airway obstruction (shunt).

$V/Q \rightarrow \infty$ = blood flow obstruction (physiologic dead space).

CO₂ transport

Carbon dioxide is transported from tissues to the lungs in 3 forms:

1. Bicarbonate (90%)



2. Bound to hemoglobin as carbaminohemoglobin (5%)
3. Dissolved CO₂ (5%)

In lungs, oxygenation of hemoglobin promotes dissociation of CO₂ from hemoglobin (Haldane effect). In peripheral tissue, $\uparrow \text{H}^+$ shifts curve to right, unloading O₂ (Bohr effect).

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

Alveolar-arterial O₂ difference

Normal alveolar-arterial O₂ difference:
 $[(A - a) \text{ DO}_2] < 10 \text{ mmHg}$.

Obstructive lung disease (COPD)

Obstruction of air flow, resulting in air trapping in the lungs. PFTs—↓ FEV₁/FVC ratio (hallmark).

Types:

1. Chronic Bronchitis (“Blue Bloater”)—productive cough for > 3 consecutive months in 2 or more years. Hypertrophy of mucus-secreting glands in the bronchioles (Reid index > 50%). Leading cause is smoking. Findings: wheezing, crackles, cyanosis.
2. Emphysema (“pink puffer”)—enlargement of air spaces and ↓ recoil resulting from destruction of alveolar walls. Caused by smoking (centriacinar emphysema) and α₁-antitrypsin deficiency (panacinar emphysema and liver cirrhosis) → ↑ elastase activity. Findings: dyspnea, ↓ breath sounds, tachycardia, ↓ I/E ratio.
3. Asthma—bronchial hyperresponsiveness causes reversible bronchoconstriction. Can be triggered by viral URIs, allergens, and stress. Findings: cough, wheezing, dyspnea, tachypnea, hypoxemia, ↓ I/E ratio, pulsus paradoxus, Curschmann’s spirals, smooth muscle hypertrophy, mucous plugging.
4. Bronchiectasis—chronic necrotizing infection of bronchi → dilated airways, purulent sputum, recurrent infections, hemoptysis. Associated with bronchial obstruction, CF, poor ciliary motility, and Kartagener’s syndrome.

Restrictive lung disease

Restricted lung expansion causes ↓ lung volumes (↓ VC and TLC). PFTs—FEV₁/FVC ratio > 80%.

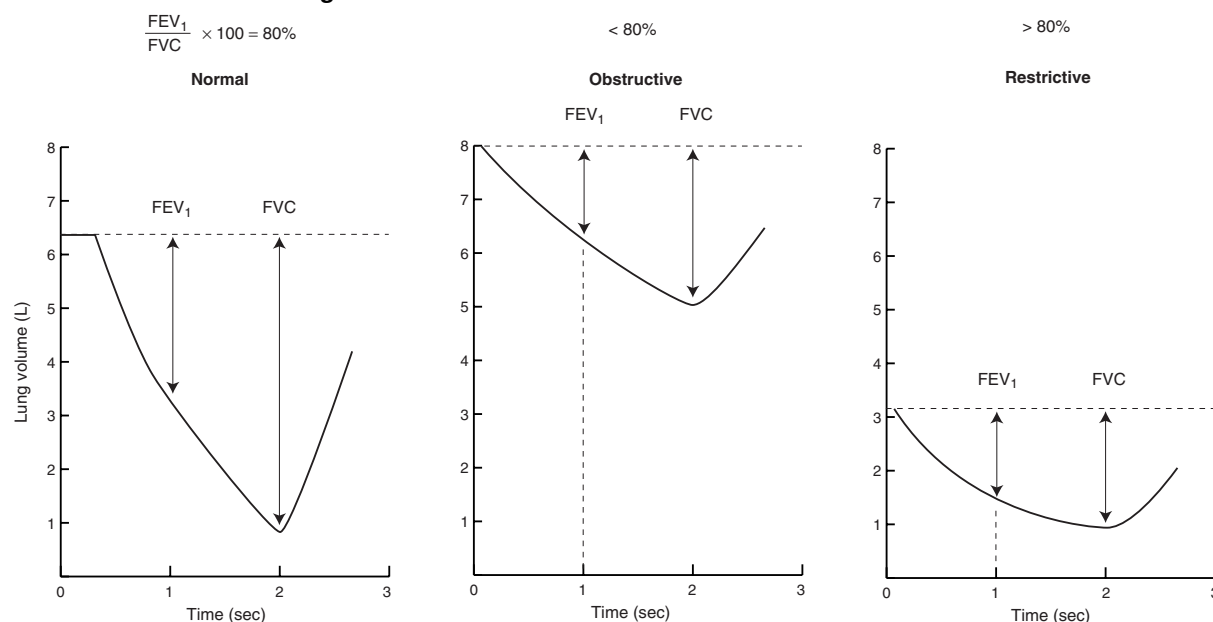
Types:

1. Poor breathing mechanics (extrapulmonary):
 - a. Poor muscular effort—polio, myasthenia gravis
 - b. Poor structural apparatus—scoliosis, morbid obesity
2. Interstitial lung diseases (pulmonary):
 - a. Adult respiratory distress syndrome (ARDS)
 - b. Neonatal respiratory distress syndrome (hyaline membrane disease)
 - c. Pneumoconioses (coal miner’s silicosis, asbestosis)
 - d. Sarcoidosis
 - e. Idiopathic pulmonary fibrosis
 - f. Goodpasture’s syndrome
 - g. Wegener’s granulomatosis
 - h. Eosinophilic granuloma

Lung—physical findings

Abnormality	Breath Sounds	Resonance	Fremitus	Tracheal Deviation
Bronchial obstruction	Absent/↓ over affected area	↓	↓	Toward side of lesion
Pleural effusion	↓ over effusion	Dullness	↓	—
Pneumonia (lobar)	May have bronchial breath sounds over lesion	Dullness	↑	—
Pneumothorax	↓	Hyperresonant	Absent	Away from side of lesion (see Color Image 40)

Obstructive vs. restrictive lung disease



Note: Obstructive lung volumes > normal (\uparrow TLC, \uparrow FRC, \uparrow RV); restrictive lung volumes < normal. In both obstructive and restrictive, FEV₁ and FVC are reduced, but in obstructive, FEV₁ is more dramatically reduced, resulting in a \downarrow FEV₁/FVC ratio.

Kartagener's syndrome

Immotile cilia due to a dynein arm defect. Results in male and female infertility (sperm immotile), bronchiectasis, and recurrent sinusitis (bacteria and particles not pushed out); associated with situs inversus.

Asbestosis

Diffuse pulmonary interstitial fibrosis caused by inhaled asbestos fibers. \uparrow risk of pleural mesothelioma and bronchogenic carcinoma. Long latency. Ferruginous bodies in lung (asbestos fibers coated with hemosiderin). Ivory-white pleural plaques (see Color Image 42).

Asbestosis and smoking greatly \uparrow risk of bronchogenic cancer (smoking not additive with mesothelioma). Seen in shipbuilders and plumbers.

Neonatal respiratory distress syndrome

Surfactant deficiency leading to \uparrow surface tension, resulting in alveolar collapse. Surfactant is made by type II pneumocytes most abundantly after 35th week of gestation. The lecithin-to-sphingomyelin ratio in the amniotic fluid, a measure of lung maturity, is usually < 1.5 in neonatal respiratory distress syndrome. Surfactant—dipalmitoyl phosphatidylcholine. Treatment: maternal steroids before birth; artificial surfactant for infant.

Lung cancer

Bronchogenic carcinoma	<p>Tumors that arise centrally:</p> <ol style="list-style-type: none"> 1. Squamous cell carcinoma—clear link to Smoking; ectopic PTH-related peptide production (see Color Image 36, Image 118) 2. Small cell carcinoma—clear link to Smoking; associated with ectopic hormone production (ADH, ACTH); may lead to Lambert-Eaton syndrome (see Color Image 37) <p>Tumors that arise peripherally:</p> <ol style="list-style-type: none"> 1. Adenocarcinoma (most common) 2. Bronchioalveolar carcinoma (thought not to be related to smoking) 3. Large cell carcinoma—undifferentiated 	<p>Small Squamous center.</p> <p>Lung cancer is the leading cause of cancer death.</p> <p>Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on x-ray.</p> <p>SPHERE of complications:</p> <ul style="list-style-type: none"> Superior vena cava syndrome Pancoast’s tumor Horner’s syndrome Endocrine (paraneoplastic) Recurrent laryngeal symptoms (hoarseness) Effusions (pleural or pericardial)
Carcinoid tumor	Can cause carcinoid syndrome (flushing, diarrhea, wheezing, and salivation).	
Metastases	Very common. Brain (epilepsy), bone (pathologic fracture), and liver (jaundice, hepatomegaly).	
Pancoast’s tumor	Carcinoma that occurs in apex of lung and may affect cervical sympathetic plexus, causing Horner’s syndrome.	Horner’s syndrome—ptosis, miosis, anhidrosis.

Pneumonia

Type	Organism(s)	Characteristics
Lobar	Pneumococcus most frequently	Intra-alveolar exudate → consolidation; may involve entire lung
Bronchopneumonia	<i>S. aureus</i> , <i>H. flu</i> , <i>Klebsiella</i> , <i>S. pyogenes</i>	Acute inflammatory infiltrates from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobes (see Image 116)
Interstitial (atypical) pneumonia	Viruses (RSV, adenoviruses), <i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i>	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; distribution involving ≥ 1 lobes (see Image 119)

Arachidonic acid products

Lipoxygenase pathway yields Leukotrienes.

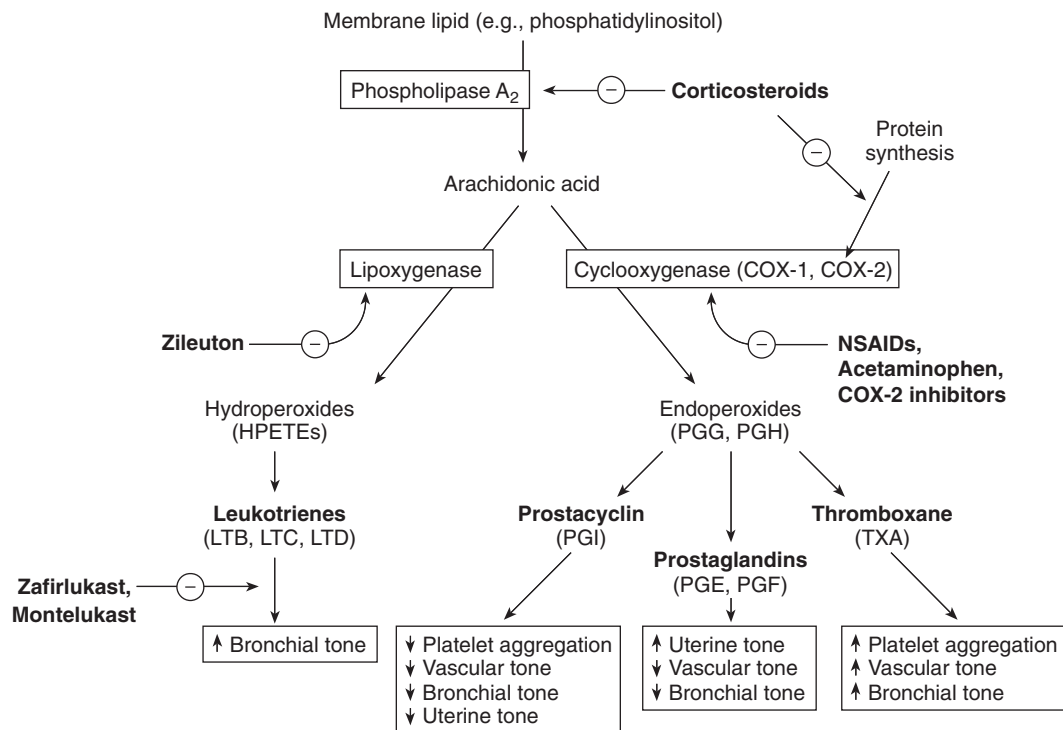
LTB₄ is a neutrophil chemotactic agent.

LTC₄, D₄, and E₄ function in bronchoconstriction, vasoconstriction, contraction of smooth muscle, and ↑ vascular permeability.

PGI₂ inhibits platelet aggregation and promotes vasodilation.

L for Lipoxygenase and Leukotriene.

Platelet-Gathering Inhibitor.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:150.)

H₁ blockers

1st generation

Clinical uses

Toxicity

2nd generation

Clinical uses

Toxicity

Reversible inhibitors of H₁ histamine receptors.

Diphenhydramine, dimenhydrinate, chlorpheniramine.

Allergy, motion sickness, sleep aid.

Sedation, antimuscarinic, anti-α-adrenergic.

Loratadine, fexofenadine, desloratadine.

Allergy.

Far less sedating than 1st generation.

Asthma drugs

Nonspecific
 β -agonists
 β_2 agonists

Isoproterenol—relaxes bronchial smooth muscle (β_2).

Adverse effect is tachycardia (β_1).

Albuterol—relaxes bronchial smooth muscle (β_2).

Use during acute exacerbation.

Salmeterol—long-acting agent for prophylaxis.

Adverse effects are tremor and arrhythmia.

Methylxanthines

Theophylline—likely causes bronchodilation by inhibiting phosphodiesterase, thereby \downarrow cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity).

Muscarinic
antagonists

Ipratropium—competitive block of muscarinic receptors, preventing bronchoconstriction.

Cromolyn

Prevents release of mediators from mast cells. Effective only for the prophylaxis of asthma. Not effective during an acute asthmatic attack. Toxicity is rare.

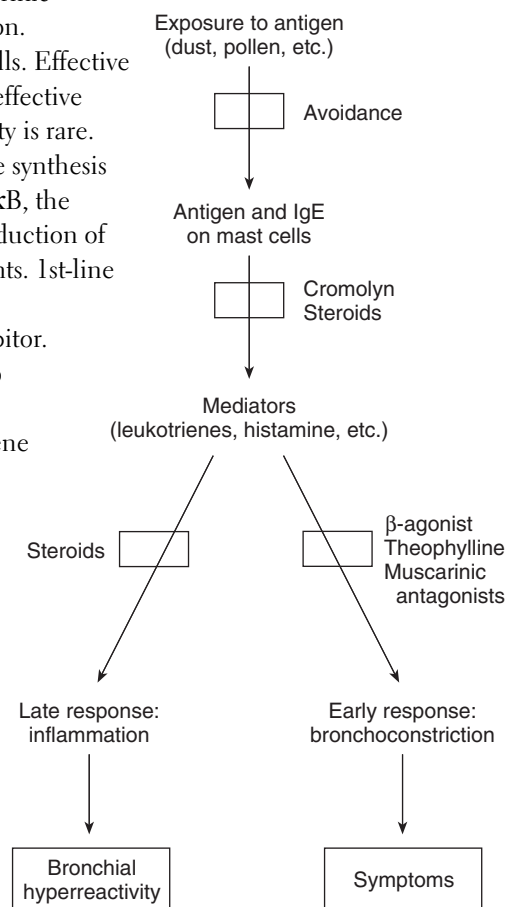
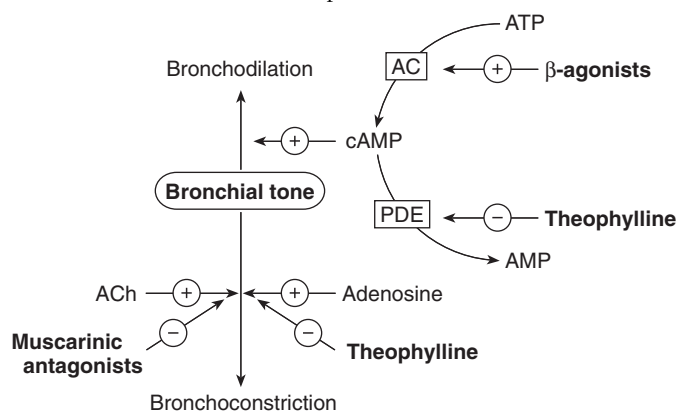
Corticosteroids

Beclomethasone, prednisone—inhibit the synthesis of virtually all cytokines. Inactivate NF- κ B, the transcription factor that induces the production of TNF- α , among other inflammatory agents. 1st-line therapy for chronic asthma.

Antileukotrienes

Zileuton—A 5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes.

Zafirlukast, montelukast—block leukotriene receptors.



Treatment strategies in asthma

(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:159 and 161.)

Rapid Review

The following tables represent a collection of high-yield associations of diseases, “buzzwords,” findings, and associated pathologies that may be useful for quick review right before the exam.

- ▶ Classic Findings
- ▶ Most Common Associations
- ▶ Equation Review

► CLASSIC FINDINGS

Disease/Finding	Association
Actinic keratosis	Often precedes squamous cell carcinoma
Addison's disease	1° adrenocortical deficiency
Albright's syndrome	Polyostotic fibrous dysplasia, precocious puberty, café-au-lait spots, short stature, young girls
Albuminocytologic dissociation	Guillain-Barré (↑ protein in CSF with only modest ↑ in cell count)
Alport's syndrome	Hereditary nephritis with nerve deafness
Anti-basement membrane antibodies	Goodpasture's syndrome
Anticentromere antibodies	Scleroderma (CREST)
Anti-double-stranded DNA antibodies (ANA antibodies)	SLE (type III hypersensitivity)
Anti-epithelial cell antibodies	Pemphigus vulgaris
Antigliadin antibodies	Celiac disease
Antihistone antibodies	Drug-induced SLE
Anti-IgG antibodies	Rheumatoid arthritis
Antimitochondrial antibodies	1° biliary cirrhosis
Antineutrophil antibodies	Vasculitis
Antiplatelet antibodies	Idiopathic thrombocytopenic purpura
Arachnodactyly	Marfan's syndrome
Argyll Robertson pupil	Neurosyphilis
Arnold-Chiari malformation	Cerebellar tonsillar herniation
Aschoff bodies	Rheumatic fever
Atrophy of the mammillary bodies	Wernicke's encephalopathy
Auer rods	Acute myelogenous leukemia (especially the promyelocytic type)
Autosplenectomy	Sickle cell anemia
Babinski's sign	UMN lesion
Baker's cyst in popliteal fossa	Rheumatoid arthritis
"Bamboo spine" on x-ray	Ankylosing spondylitis
Bartter's syndrome	Hyperreninemia
Basophilic stippling of RBCs	Lead poisoning
Becker's muscular dystrophy	Defective dystrophin; less severe than Duchenne's
Bell's palsy	LMN CN VII palsy
Bence Jones proteins	Multiple myeloma (kappa or lambda Ig light chains in urine), Waldenström's macroglobulinemia (IgM)

Berger's disease	IgA nephropathy
Bernard-Soulier disease	Defect in platelet adhesion
Bilateral hilar adenopathy, uveitis	Sarcoidosis
Birbeck granules on EM	Histiocytosis X (eosinophilic granuloma)
Bloody tap on LP	Subarachnoid hemorrhage
"Blue bloater"	Chronic bronchitis
Blue-domed cysts	Fibrocystic change of the breast
Blue sclera	Osteogenesis imperfecta
Boot-shaped heart on x-ray	Tetralogy of Fallot; RVH
Bouchard's nodes	Osteoarthritis (PIP swelling 2° to osteophytes)
Boutonnière deformity	Rheumatoid arthritis
Branching rods in oral infection	<i>Actinomyces israelii</i>
"Brown tumor" of bone	Hemorrhage causes brown color of osteolytic cysts: 1. Hyperparathyroidism 2. Osteitis fibrosa cystica (von Recklinghausen's disease)
Brushfield's spots	Down syndrome
Bruton's disease	X-linked agammaglobulinemia
Budd-Chiari syndrome	Posthepatic venous thrombosis
Buerger's disease	Small/medium-artery vasculitis
Burkitt's lymphoma	8:14 translocation; associated with EBV
Burton's lines	Lead poisoning
C-ANCA, P-ANCA	Wegener's granulomatosis, polyarteritis nodosa
Café-au-lait spots on skin	Neurofibromatosis
Caisson disease	Gas emboli
Calf pseudohypertrophy	Duchenne's muscular dystrophy
Call-Exner bodies	Granulosa-theca cell tumor of the ovary
Cardiomegaly with apical atrophy	Chagas' disease
Cerebriform nuclei	Mycosis fungoides (cutaneous T-cell lymphoma)
Chagas' disease	Trypanosome infection
Chancre	1° syphilis (not painful)
Chancroid	<i>Haemophilus ducreyi</i> (painful)
Charcot's triad	Multiple sclerosis (nystagmus, intention tremor, scanning speech), cholangitis (jaundice, RUQ pain, fever)
Charcot-Leyden crystals	Bronchial asthma (eosinophil membranes)
Chédiak-Higashi disease	Phagocyte deficiency

► CLASSIC FINDINGS (continued)

Cherry-red spot on macula	Tay-Sachs, Niemann-Pick disease, central retinal artery occlusion
Cheyne-Stokes respirations	Central apnea in CHF and ↑ intracranial pressure
“Chocolate cysts”	Endometriosis (frequently involves both ovaries)
Chronic atrophic gastritis	Predisposition to gastric carcinoma
Chvostek’s sign	Hypocalcemia (facial muscle spasm upon tapping)
Clear cell adenocarcinoma of the vagina	DES exposure in utero
Clue cells	<i>Gardnerella vaginitis</i>
Codman’s triangle on x-ray	Osteosarcoma
Cold agglutinins	<i>Mycoplasma pneumoniae</i> , infectious mononucleosis
Cold intolerance	Hypothyroidism
Condylomata lata	2° syphilis
Continuous machinery murmur	Patent ductus arteriosus
Cori’s disease	Debranching enzyme deficiency
Cotton-wool spots	Chronic hypertension
Cough, conjunctivitis, coryza + fever	Measles
Councilman bodies	Toxic or viral hepatitis
Cowdry type A bodies	Herpesvirus
Crescents in Bowman’s capsule	Rapidly progressive crescentic glomerulonephritis
Crigler-Najjar syndrome	Congenital unconjugated hyperbilirubinemia
Curling’s ulcer	Acute gastric ulcer associated with severe burns
Currant-jelly sputum	<i>Klebsiella</i>
Curschmann’s spirals	Bronchial asthma (whorled mucous plugs)
Cushing’s ulcer	Acute gastric ulcer associated with CNS injury
D-dimers	DIC
Depigmentation of neurons in substantia nigra	Parkinson’s disease (basal ganglia disorder—rigidity, resting tremor, bradykinesia)
Dermatitis, dementia, diarrhea	Pellagra (niacin, vitamin B ₃ deficiency)
Diabetes insipidus + exophthalmos + lesions of skull	Hand-Schüller-Christian disease
Dog or cat bite	<i>Pasteurella multocida</i>
Donovan bodies	Granuloma inguinale
Dressler’s syndrome	Post-MI fibrinous pericarditis

Dubin-Johnson syndrome	Congenital conjugated hyperbilirubinemia (black liver)
Duchenne's muscular dystrophy	Deleted dystrophin gene (X-linked recessive)
Eburnation	Osteoarthritis (polished, ivory-like appearance of bone)
Edwards' syndrome	Trisomy 18 associated with rocker-bottom feet, low-set ears, heart disease
Eisenmenger's complex	Late cyanosis shunt (uncorrected L → R shunt becomes R → L shunt)
Elastic skin	Ehlers-Danlos syndrome
Erb-Duchenne palsy	Superior trunk brachial plexus injury ("waiter's tip")
Erythema chronicum migrans	Lyme disease
Fanconi's syndrome	Proximal tubular reabsorption defect
"Fat, female, forty, and fertile"	Acute cholecystitis
Fatty liver	Alcoholism
Ferruginous bodies	Asbestosis
Gardner's syndrome	Colon polyps with osteomas and soft tissue tumors
Gaucher's disease	Glucocerebrosidase deficiency
Ghon focus	1° TB
Gilbert's syndrome	Benign congenital unconjugated hyperbilirubinemia
Glanzmann's thrombasthenia	Defect in platelet aggregation
Goodpasture's syndrome	Autoantibodies against alveolar and glomerular basement membrane proteins
Gowers' maneuver	Duchenne's (use of patient's arms to help legs pick self off the floor)
Guillain-Barré syndrome	Idiopathic polyneuritis
"Hair-on-end" appearance on x-ray	β-thalassemia, sickle cell anemia (extramedullary hematopoiesis)
Hand-Schüller-Christian disease	Chronic progressive histiocytosis
HbF	Thalassemia major
HbS	Sickle cell anemia
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo)
Heberden's nodes	Osteoarthritis (DIP swelling 2° to osteophytes)
Heinz bodies	G6PD deficiency
Henoch-Schönlein purpura	Hypersensitivity vasculitis associated with hemorrhagic urticaria and URIs
Heterophil antibodies	Infectious mononucleosis (EBV)
High-output cardiac failure (dilated cardiomyopathy)	Wet beriberi (thiamine, vitamin B ₁ deficiency)
HLA-B27	Reiter's syndrome, ankylosing spondylitis
HLA-DR3 or -DR4	Diabetes mellitus type 1 (caused by autoimmune destruction of β cells)
Homer Wright rosettes	Neuroblastoma
Honeycomb lung on x-ray	Interstitial fibrosis

► CLASSIC FINDINGS (*continued*)

Horner's syndrome	Ptosis, miosis, and anhidrosis
Howell-Jolly bodies	Splenectomy (or nonfunctional spleen)
Huntington's disease	Caudate degeneration (autosomal dominant)
Hyperphagia + hypersexuality + hyperorality + hyperdocility	Klüver-Bucy syndrome (amygdala)
Hyperpigmentation of skin	1° adrenal insufficiency (Addison's disease)
Hypersegmented neutrophils	Macrocytic anemia
Hypertension + hypokalemia	Conn's syndrome
Hypochromic microcytosis	Iron deficiency anemia, lead poisoning
Increased α -fetoprotein in amniotic fluid/maternal serum	Anencephaly, spina bifida (neural tube defects)
Increased uric acid levels	Gout, Lesch-Nyhan syndrome, myeloproliferative disorders, loop and thiazide diuretics
Intussusception	Adenovirus (causes hyperplasia of Peyer's patches)
Janeway lesions	Endocarditis
Jarisch-Herxheimer reaction	Syphilis—overaggressive treatment of an asymptomatic patient that causes symptoms due to rapid lysis
Job's syndrome	Neutrophil chemotaxis abnormality
Kaposi's sarcoma	AIDS in MSM (men who have sex with men)
Kartagener's syndrome	Dynein defect
Kayser-Fleischer rings	Wilson's disease
Keratin pearls	Squamous cell carcinoma
Kimmelstiel-Wilson nodules	Diabetic nephropathy
Klüver-Bucy syndrome	Bilateral amygdala lesions
Koilocytes	HPV
Koplik spots	Measles
Krukenberg tumor	Gastric adenocarcinoma with ovarian metastases
Kussmaul hyperpnea	Diabetic ketoacidosis
Lens dislocation + aortic dissection + joint hyperflexibility	Marfan's syndrome (fibrillin deficit)
Lesch-Nyhan syndrome	HGPRT deficiency
Lewy bodies	Parkinson's disease
Libman-Sacks disease	Endocarditis associated with SLE
Lines of Zahn	Arterial thrombus
Lisch nodules	Neurofibromatosis (von Recklinghausen's disease)

Low serum ceruloplasmin	Wilson's disease
Lucid interval	Epidural hematoma
"Lumpy-bumpy" appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis
Lytic bone lesions on x-ray	Multiple myeloma
Mallory bodies	Alcoholic liver disease
Mallory-Weiss syndrome	Esophagogastric lacerations
McArdle's disease	Muscle phosphorylase deficiency
McBurney's sign	Appendicitis
MLF syndrome (INO)	Multiple sclerosis
Monoclonal antibody spike	Multiple myeloma (called the M protein; usually IgG or IgA), MGUS (monoclonal gammopathy of undetermined significance), Waldenström's (M protein = IgM) macroglobulinemia
Myxedema	Hypothyroidism
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Wegener's and Goodpasture's (hemoptysis and glomerular disease)
Needle-shaped, negatively birefringent crystals	Gout
Negri bodies	Rabies
Nephritis + cataracts + hearing loss	Alport's syndrome
Neurofibrillary tangles	Alzheimer's disease
Niemann-Pick disease	Sphingomyelinase deficiency
No lactation postpartum	Sheehan's syndrome (pituitary infarction)
Nutmeg liver	CHF
Occupational exposure to asbestos	Malignant mesothelioma
"Orphan Annie" nuclei	Papillary carcinoma of the thyroid
Osler's nodes	Endocarditis
Owl's eye	CMV
Painless jaundice	Pancreatic cancer (head)
Palpable purpura on legs and buttocks	Henoch-Schönlein purpura
Pancoast's tumor	Bronchogenic apical tumor associated with Horner's syndrome
Pannus	Rheumatoid arthritis
Parkinson's disease	Nigrostriatal dopamine depletion
Periosteal elevation on x-ray	Pyogenic osteomyelitis
Peutz-Jeghers syndrome	Benign polyposis
Peyronie's disease	Penile fibrosis

► CLASSIC FINDINGS (continued)

Philadelphia chromosome (<i>bcr-abl</i>)	CML (may sometimes be associated with AML)
Pick bodies	Pick's disease
Pick's disease	Progressive dementia, similar to Alzheimer's
"Pink puffer"	Emphysema (centroacinar [smoking], panacinar [α_1 -antitrypsin deficiency])
Plummer-Vinson syndrome	Esophageal webs with iron deficiency anemia
Podagra	Gout (MP joint of hallux)
Podocyte fusion	Minimal change disease
Polyneuropathy, cardiac pathology, and edema	Dry beriberi (thiamine, vitamin B ₁ deficiency)
Polyneuropathy preceded by GI or respiratory infection	Guillain-Barré syndrome
Pompe's disease	Lysosomal glucosidase deficiency associated with cardiomegaly
Port-wine stain	Hemangioma
Positive anterior "drawer sign"	Anterior cruciate ligament injury
Pott's disease	Vertebral tuberculosis
Pseudopalisade tumor cell arrangement	Glioblastoma multiforme
Pseudorosettes	Ewing's sarcoma
Ptosis, miosis, anhidrosis	Horner's syndrome (Pancoast's tumor)
Rash on palms and soles	2° syphilis, Rocky Mountain spotted fever
Raynaud's syndrome	Recurrent vasospasm in extremities
RBC casts in urine	Acute glomerulonephritis
Recurrent pulmonary <i>Pseudomonas</i> and <i>S. aureus</i> infections	Cystic fibrosis
Red urine in the morning	Paroxysmal nocturnal hemoglobinuria
Reed-Sternberg cells	Hodgkin's lymphoma
Reid index (increased)	Chronic bronchitis
Reinke crystals	Leydig cell tumor
Reiter's syndrome	Urethritis, conjunctivitis, arthritis
Renal cell carcinoma + cavernous hemangiomas + adenomas	von Hippel-Lindau disease
Renal epithelial casts in urine	Acute toxic/viral nephrosis
Rhomboid crystals, positively birefringent	Pseudogout

Rib notching	Coarctation of aorta
Roth's spots in retina	Endocarditis
Rotor's syndrome	Congenital conjugated hyperbilirubinemia
Rouleaux formation (RBCs)	Multiple myeloma
Russell bodies	Multiple myeloma
S3	Left-to-right shunt (VSD, PDA, ASD), mitral regurgitation, LV failure (CHF)
S4	Aortic stenosis, hypertrophic subaortic stenosis
Schiller-Duval bodies	Yolk sac tumor
Senile plaques	Alzheimer's disease
Sézary syndrome	Cutaneous T-cell lymphoma
Sheehan's syndrome	Postpartum pituitary necrosis
Shwartzman reaction	<i>Neisseria meningitidis</i>
Signet-ring cells	Gastric carcinoma
Simian crease	Down syndrome
Sipple's syndrome	MEN type IIa
Sjögren's syndrome	Dry eyes, dry mouth, arthritis
Skip lesions	Crohn's
Slapped cheeks	Erythema infectiosum (fifth disease)
Smith antigen	SLE
"Smudge cell"	CLL
Soap bubble on x-ray	Giant cell tumor of bone
Spike and dome on EM	Membranous glomerulonephritis
Spitz nevus	Benign juvenile melanoma
Splinter hemorrhages in fingernails	Endocarditis
Starry-sky pattern	Burkitt's lymphoma
"Strawberry tongue"	Scarlet fever
Streaky ovaries	Turner's syndrome
String sign on x-ray	Crohn's disease
Subepithelial humps on EM	Poststreptococcal glomerulonephritis
Suboccipital lymphadenopathy	Rubella
Sulfur granules	<i>Actinomyces israelii</i>
Swollen gums, bruising, poor wound healing, anemia	Scurvy (ascorbic acid, vitamin C deficiency)—vitamin C is necessary for hydroxylation of proline and lysine in collagen synthesis
Systolic ejection murmur (crescendo-decrescendo)	Aortic valve stenosis

► CLASSIC FINDINGS (continued)

t(8;14)	Burkitt's lymphoma (<i>c-myc</i> activation)
t(9;22)	Philadelphia chromosome, CML (<i>bcr-abl</i> hybrid)
t(14;18)	Follicular lymphomas (<i>bcl-2</i> activation)
Tabes dorsalis	3° syphilis
Tendon xanthomas (classically Achilles)	Familial hypercholesterolemia
Thumb sign on lateral x-ray	Epiglottitis (<i>Haemophilus influenzae</i>)
Thyroidization of kidney	Chronic bacterial pyelonephritis
Tophi	Gout
"Tram-track" appearance on LM	Membranoproliferative glomerulonephritis
Trousseau's sign	Visceral cancer, pancreatic adenocarcinoma (migratory thrombophlebitis), hypocalcemia (carpal spasm)
Virchow's node	Left supraclavicular node enlargement from metastatic carcinoma of the stomach
Virchow's triad	Pulmonary embolism (triad = blood stasis, endothelial damage, hypercoagulation)
von Recklinghausen's disease	Neurofibromatosis with café-au-lait spots
von Recklinghausen's disease of bone	Osteitis fibrosa cystica ("brown tumor")
Wallenberg's syndrome	PICA thrombosis
Waterhouse-Friderichsen syndrome	Adrenal hemorrhage associated with meningococemia
Waxy casts	Chronic end-stage renal disease
WBC casts in urine	Acute pyelonephritis
WBCs in urine	Acute cystitis
Wermer's syndrome	MEN type I
Whipple's disease	Malabsorption syndrome caused by <i>Tropheryma whippelii</i>
Wilson's disease	Hepatolenticular degeneration
"Wire loop" appearance on LM	Lupus nephropathy
"Worst headache of my life"	Berry aneurysm—associated with adult polycystic kidney disease
Xanthochromia (CSF)	Subarachnoid hemorrhage
Xerostomia + arthritis + keratoconjunctivitis sicca	Sjögren's syndrome
Zenker's diverticulum	Upper GI diverticulum
Zollinger-Ellison syndrome	Gastrin-secreting tumor associated with ulcers

MOST COMMON ASSOCIATIONS

Most Common ...	
Bacteremia/pneumonia (IVDA)	<i>S. aureus</i>
Bacteria associated with cancer	<i>H. pylori</i>
Bacteria found in GI tract	<i>Bacteroides</i> (second most common is <i>E. coli</i>)
Brain tumor (adults)	Mets > astrocytoma (including glioblastoma multiforme) > meningioma > schwannoma
Brain tumor (kids)	Medulloblastoma (cerebellum)
Brain tumor—supratentorial (kids)	Craniopharyngioma
Breast cancer	Infiltrating ductal carcinoma (in the United States, 1 in 9 women will develop breast cancer)
Breast mass	Fibrocystic change (in postmenopausal women, carcinoma is the most common)
Breast tumor (benign)	Fibroadenoma
Bug in debilitated, hospitalized pneumonia patient	<i>Klebsiella</i>
Cardiac 1° tumor (adults)	Myxoma (4:1 left to right atrium; “ball and valve”)
Cardiac 1° tumor (kids)	Rhabdomyoma
Cardiac tumor (adults)	Mets
Cardiomyopathy	Dilated cardiomyopathy
Chromosomal disorder	Down syndrome (associated with ALL, Alzheimer’s dementia, and endocardial cushion defects)
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)
Congenital cardiac anomaly	VSD
Constrictive pericarditis	Tuberculosis
Coronary artery involved in thrombosis	LAD > RCA > LCA
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus
Cyanosis (late; more common)	VSD, ASD, PDA (close with indomethacin; open with misoprostol)
Demyelinating disease	Multiple sclerosis
Dietary deficit	Iron
Epiglottitis	<i>Haemophilus influenzae</i> type B
Esophageal cancer	Squamous cell carcinoma
Gene involved in cancer	p53 tumor suppressor gene
Group affected by cystic fibrosis	Caucasians (fat-soluble vitamin deficiencies, mucous plugs/lung infections)
Gynecologic malignancy	Endometrial carcinoma
Heart murmur	Mitral valve prolapse

► MOST COMMON ASSOCIATIONS (*continued*)

Heart valve in bacterial endocarditis	Mitral
Heart valve in bacterial endocarditis in IVDA	Tricuspid
Heart valve (rheumatic fever)	Mitral valve (aortic is 2nd)
Helminth infection (U.S.)	<i>Enterobius vermicularis</i> (<i>Ascaris lumbricoides</i> is 2nd most common)
Hereditary bleeding disorder	von Willebrand's
Kidney stones	Calcium = radiopaque (2nd most common is ammonium = radiopaque; formed by urease-positive organisms such as <i>Proteus vulgaris</i> or <i>Staphylococcus</i>)
Liver disease	Alcoholic liver disease
Location of brain tumors (adults)	Supratentorial
Location of brain tumors (kids)	Infratentorial
Lysosomal storage disease	Gaucher's disease
Male cancer	Prostatic carcinoma
Malignancy associated with noninfectious fever	Hodgkin's disease
Malignant skin tumor	Basal cell carcinoma (rarely metastasizes)
Mets to bone	Breast, lung, thyroid, testes, prostate, kidney
Mets to brain	Lung, breast, skin (melanoma), kidney (renal cell carcinoma), GI
Mets to liver	Colon, gastric, pancreatic, breast, and lung carcinomas
Motor neuron disease	ALS
Neoplasm (kids)	ALL (2nd most common is cerebellar medulloblastoma)
Nephrotic syndrome	Membranous glomerulonephritis
Obstruction of male urinary tract	BPH
Opportunistic infection in AIDS	<i>Pneumocystis carinii</i> pneumonia
Organ receiving mets	Adrenal glands (due to rich blood supply)
Organ sending mets	Lung > breast, stomach
Ovarian tumor (benign)	Serous cystadenoma
Ovarian tumor (malignant)	Serous cystadenocarcinoma
Pancreatic tumor	Adenocarcinoma (head of pancreas)
Patient with ALL/CLL/AML/CML	ALL—child, CLL—adult > 60, AML—adult > 60, CML—adult 35–50
Patient with Hodgkin's	Young male (except nodular sclerosis type—female)
Patient with minimal change disease	Young child
Patient with Reiter's	Male
Pituitary tumor	Prolactinoma (2nd—somatotrophic "acidophilic" adenoma)

Preventable cancer	Lung cancer
Primary bone tumor (adults)	Multiple myeloma
Primary hyperparathyroidism	Adenomas (followed by hyperplasia, then carcinoma)
Primary liver tumor	Hepatoma
Renal tumor	Renal cell carcinoma—associated with von Hippel–Lindau and acquired polycystic kidney disease; paraneoplastic syndromes (erythropoietin, renin, PTH, ACTH)
Secondary hyperparathyroidism	Hypocalcemia of chronic renal failure
Sexually transmitted disease	<i>Chlamydia</i>
Site of diverticula	Sigmoid colon
Site of metastasis	Regional lymph nodes
Site of metastasis (2nd most common)	Liver
Sites of atherosclerosis	Abdominal aorta > coronary > popliteal > carotid
Skin cancer	Basal cell carcinoma
Stomach cancer	Adenocarcinoma
Testicular tumor	Seminoma
Thyroid cancer	Papillary carcinoma
Tracheoesophageal fistula	Lower esophagus joins trachea/upper esophagus—blind pouch
Tumor in men	Prostate carcinoma
Tumor in women	Leiomyoma (estrogen dependent)
Tumor of infancy	Hemangioma
Tumor of the adrenal medulla (adults)	Pheochromocytoma (benign)
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)
Type of Hodgkin's	Nodular sclerosis (vs. mixed cellularity, lymphocytic predominance, lymphocytic depletion)
Type of non-Hodgkin's	Follicular, small cleaved
Type of pituitary adenoma	Prolactinoma
Vasculitis	Temporal arteritis (risk of ipsilateral blindness due to thrombosis of ophthalmic artery)
Viral encephalitis	HSV
Vitamin deficiency (U.S.)	Folic acid (pregnant women are at high risk; body stores only 3- to 4-month supply)

► MOST COMMON ASSOCIATIONS (*continued*)

Most Frequent Cause of ...	
Addison's	Autoimmune (infection is the 2nd most common cause)
Aneurysm, dissecting	Hypertension
Aortic aneurysm, abdominal and descending aorta	Atherosclerosis
Aortic aneurysm, ascending	3° syphilis
Bacterial meningitis (adults)	<i>Neisseria meningitidis</i>
Bacterial meningitis (elderly)	<i>Streptococcus pneumoniae</i>
Bacterial meningitis (kids)	<i>Haemophilus influenzae</i> type B
Bacterial meningitis (newborns)	<i>E. coli</i>
Cancer associated with AIDS	Kaposi's sarcoma
Congenital adrenal hyperplasia	21-hydroxylase deficiency
Cretinism	Iodine deficit/hypothyroidism
Cushing's syndrome	Corticosteroid therapy (2nd most common cause is excess ACTH secretion by pituitary)
Death in CML	Blast crisis
Death in SLE	Lupus nephropathy
Dementia	Alzheimer's (2nd most common is multi-infarct)
DIC	Gram-negative sepsis, obstetric complications, cancer, burn trauma
Ejection click	Aortic/pulmonic stenosis
Food poisoning	<i>S. aureus</i>
Glomerulonephritis (adults)	IgA nephropathy (Berger's disease)
Hematoma—epidural	Rupture of middle meningeal artery (arterial bleeding is fast)
Hematoma—subdural	Rupture of bridging veins (trauma; venous bleeding is slow)
Hemochromatosis	Multiple blood transfusions (can result in CHF and ↑ risk of hepatocellular carcinoma)
Hepatic cirrhosis	EtOH
Hepatocellular carcinoma	Cirrhotic liver (often associated with hepatitis B and C)
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation
Hypertension, 2°	Renal disease
Hypoparathyroidism	Thyroidectomy
Hypopituitarism	Adenoma
Infection in blood transfusion	Hepatitis C
Infection in burn victims	<i>Pseudomonas</i>

Leukemia (adults)	AML
"Machine-like" murmur	PDA
Mental retardation	Down syndrome (fragile X is the second most common cause)
MI	Atherosclerosis
Mitral valve stenosis	Rheumatic heart disease
Myocarditis	Coxsackie B
Nephrotic syndrome (adults)	Membranous glomerulonephritis
Nephrotic syndrome (kids)	Minimal change disease (associated with infections/vaccinations; treat with corticosteroids)
Opening snap	Mitral stenosis
Osteomyelitis	<i>S. aureus</i>
Osteomyelitis in patients with sickle cell disease	<i>Salmonella</i>
Osteomyelitis with IVDA	<i>Pseudomonas</i>
Pancreatitis (acute)	EtOH and gallstones
Pancreatitis (chronic)	EtOH (adults), cystic fibrosis (kids)
Peau d'orange	Carcinoma of the breast
PID	<i>Neisseria gonorrhoeae</i> (monoarticular arthritis)
Pneumonia, hospital-acquired	<i>Klebsiella</i>
Pneumonia in cystic fibrosis, burn infection	<i>Pseudomonas aeruginosa</i>
Preventable blindness	<i>Chlamydia</i>
Primary amenorrhea	Turner's (XO)
Primary hyperaldosteronism	Adenoma of adrenal cortex
Primary hyperparathyroidism	Adenoma
Pulmonary hypertension	COPD
Right heart failure due to a pulmonary cause	Cor pulmonale
Right-sided heart failure	Left-sided heart failure
Sheehan's syndrome	Postpartum pituitary infarction 2° to hemorrhage
SIADH	Small cell carcinoma of the lung
UTI	<i>E. coli</i>
UTI (young women)	<i>E. coli</i> and <i>Staphylococcus saprophyticus</i>

Topic	Equation	Page
Sensitivity	$\text{Sensitivity} = \frac{a}{a + c}$	63
Specificity	$\text{Specificity} = \frac{d}{b + d}$	63
Positive predictive value	$\text{PPV} = \frac{a}{a + b}$	63
Negative predictive value	$\text{NPV} = \frac{d}{c + d}$	63
Relative risk	$\text{RR} = \frac{\left[\frac{a}{a + b} \right]}{\left[\frac{c}{c + d} \right]}$	63
Attributable risk	$\text{AR} = \left[\frac{a}{a + b} \right] - \left[\frac{c}{c + d} \right]$	63
Hardy-Weinberg equilibrium	$p^2 + 2pq + q^2 = 1$ $p + q = 1$	106
Henderson-Hasselbalch equation	$\text{pH} = \text{pKa} + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ Pco}_2}$	382
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	195
Clearance	$\text{CL} = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}}$	195
Half-life	$t_{1/2} = \frac{0.7 \times V_d}{\text{CL}}$	195
Loading dose	$\text{LD} = C_p \times \frac{V_d}{F}$	195
Maintenance dose	$\text{MD} = C_p \times \frac{\text{CL}}{F}$	195
Cardiac output	$\text{CO} = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$	218
Cardiac output	$\text{CO} = \text{stroke volume} \times \text{heart rate}$	218
Mean arterial pressure	$\text{MAP} = \text{cardiac output} \times \text{total peripheral resistance}$	218
Mean arterial pressure	$\text{MAP} = \frac{1}{3} \text{ systolic} + \frac{2}{3} \text{ diastolic}$	218
Stroke volume	$\text{SV} = \text{end diastolic volume} - \text{end systolic volume}$	218
Ejection fraction	$\text{EF} = \frac{\text{stroke volume}}{\text{end diastolic volume}} \times 100$	219
Resistance	$R = \frac{\text{driving pressure}}{\text{flow}} = \frac{8\eta (\text{viscosity}) \times \text{length}}{\pi r^4}$	219
Net filtration pressure	$P_{\text{net}} = [(P_c - P_i) - (\pi_c - \pi_i)]$	227

Glomerular filtration rate	$GFR = U_{\text{inulin}} \times \frac{V}{P_{\text{inulin}}} = C_{\text{inulin}}$	377
Glomerular filtration rate	$GFR = K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	377
Effective renal plasma flow	$ERPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	377
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	377
Filtration fraction	$FF = \frac{GFR}{RPF}$	378
Free water clearance	$C_{H_2O} = V - C_{osm}$	378
Physiologic dead space	$V_D = V_T \times \frac{(Paco_2 - Peco_2)}{Paco_2}$	413

This image shows a full page of blank, lined paper. It features approximately 28 horizontal blue or grey lines spaced evenly apart, typical of notebook paper. The lines extend across the entire width of the page, leaving small margins at the top and bottom. There are no vertical lines, text, or other markings on the page.

SECTION IV

Top-Rated Review Resources

- ▶ How to Use the Database
- ▶ World Wide Web Sites
- ▶ Comprehensive
- ▶ Anatomy
- ▶ Behavioral Science
- ▶ Biochemistry
- ▶ Microbiology and Immunology
- ▶ Pathology
- ▶ Pharmacology
- ▶ Physiology
- ▶ Commercial Review Courses
- ▶ Publisher Contacts

This section is a database of top-rated basic science review books, sample examination books, software, Web sites, and commercial review courses that have been marketed to medical students studying for the USMLE Step 1. At the end of the section is a list of publishers and independent bookstores with addresses and phone numbers. For each book, we list the **Title** of the book, the **First Author** (or editor), the **Series Name** (where applicable), the **Current Publisher**, the **Copyright Year**, the **Number of Pages**, the **ISBN Code**, the **Approximate List Price**, the **Format** of the resource, and the **Number of Test Questions**. The entries for most books also include **Summary Comments** that describe their style and overall utility for studying. Finally, each book receives a **Rating**. Books are sorted into a comprehensive section as well as into sections corresponding to the seven traditional basic medical science disciplines (anatomy, behavioral science, biochemistry, microbiology and immunology, pathology, pharmacology, and physiology). Within each section, books are arranged first by Rating and then alphabetically by First Author within each Rating group.

For the 2006 edition of *First Aid for the*® *USMLE Step 1*, the database of rated review books has been reorganized and updated with the addition of many new books and software and with the removal of some older, outdated items. A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better sources.
B–	Fair, but there are many better books in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in preparing for the USMLE Step 1 examination. This is based on a number of factors, including:

- The cost
- The readability of the text
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (e.g., graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1 examination

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1 examination. Many books with lower ratings are well written and informative but are not ideal for boards preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publishers' prices change frequently.
- Bookstores often charge an additional markup.
- New editions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. (See p. xvii, How to Contribute.) In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer-based tutorials, commercial review courses, and World Wide Web sites.

Disclaimer/Conflict of Interest Statement

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through the publisher. Please note that the entire Underground Clinical Vignette series are independent publications by the authors of this book; their ratings are based solely on data from the student survey and feedback forms.

A

Kaplan Medical (Qbank)

KAPLAN

www.kaplanmedical.com

An Internet-based question bank providing tailored boards-format exams. Test content and performance feedback are provided by organ system and discipline. Questions are similar in style and content to those on the actual exam. Includes well-written, detailed explanations. Costs vary with subscription period but are generally high. A physiology-specific Qbank with more than 750 questions is also available, as is an Integrated Clinical Vignettes Qbank with more than 1200 clinical case-based boards review questions. Requires considerable time commitment.

\$199 for one month;

\$279 for three months

Test/2000+ q

A

WebPath: The Internet Pathology Laboratory

KLATT

<http://www-medlib.med.utah.edu/WebPath/webpath.html>

Features a wealth of outstanding gross and microscopic illustrations, clinical vignette questions, and case studies. Contains many classic, high-quality illustrations. Includes 8 general pathology exams and 11 system-based exams with a total of more than 800 questions. Also includes 170 questions associated with images. Questions reflect current boards format and difficulty level but are typically shorter. A WebPath CD-ROM is available for \$60.00 and features the online Web site plan supplemented with additional illustrations, topics, tutorials, and radiology. The CD-ROM is ideal for computers with slow or no Internet access.

Free

Review/1000+ q

A-

Digital Anatomist Interactive Atlases

UNIVERSITY OF WASHINGTON

www9.biostr.washington.edu/da.html

A good site containing an interactive neuroanatomy course along with a three-dimensional atlas of the brain, thorax, and knee. Atlases have computer-generated images along with cadaver dissections. Each atlas also has a useful quiz in which users identify structures in the slide images. An excellent source for reviewing neuro images.

Free

Review

A ⁻	<p><i>The Pathology Guy</i> FRIEDLANDER www.pathguy.com A free Web site containing extensive but poorly organized information on a variety of fundamental concepts in pathology. Excellent collection of high-yield facts in “Ed’s Pathology Review for USMLE,” which is buried at the end of each pathology topic page. Philosophical and religious digressions can impede a rapid review of the site.</p>	Free	Review
B ⁺	<p><i>Blackwell’s Step 1 Online Q&A</i> CLEMENT Blackwell Science www.blackwellusmle.com A full-length, seven-block, 350-question practice exam in a format similar to that of the real exam. Questions come with explanations related to the selected answer only. The user can bookmark questions and can take the test all at once or by section. Limited student feedback.</p>	Free	Test/350 q
B ⁺	<p><i>Introduction to Clinical Microbiology</i> http://medic.med.uth.tmc.edu/path/00001450.htm A basic introduction to and review of the fundamentals of microbiology. Includes a useful review of the different types of culture media and lab tests. The information on bugs is a shallow but quick read.</p>	Free	Review
B	<p><i>The Whole Brain Atlas</i> JOHNSON www.med.harvard.edu/AANLIB/home.html A collection of high-quality brain MR and CT images with views of normal, aging, and diseased brains (CVA, degenerative, neoplastic, and inflammatory diseases). The interface is technologically impressive but complex. Guided tours and image correlations to cases are especially useful. Although not all of the images are particularly high yield for the boards, this is an excellent introduction to neuroimaging.</p>	Free	Review
B	<p><i>USMLEasy</i> MCGRAW-HILL www.usmleasy.com An Internet-based question bank based on the <i>PreTest</i> series consisting of approximately 2800 questions. Requires an online subscription. Some questions are more obscure than those appearing on the actual exam. Users can track questions completed as well as customize tests. Presented in boards format. Useful as a supplemental review after other resources have been exhausted.</p>	\$99 for one month; \$199 for three months	Test/2800 q

B-**Active Learning Centre****Free**

Test/100 q

TURCHINwww.med.jhu.edu/medcenter/quiz/home.cgi

A quiz engine site based on a large database with an extensive list of bugs, drugs, and vaccines. Questions generated test the basic characteristics of each element in the database in a multiple-choice, matching, or essay format that the user selects. Questions are not boards style but are useful for learning the memory-intensive subjects of microbiology and pharmacology.

A⁻***Kaplan's USMLE Step 1 Home Study Program*****\$449.00**

Review/1200 q

KAPLAN

Kaplan, 2005, ISBN 0X63410105

Includes two organ system–based review books, a test-taking and strategy guide, a Qbook of 850 questions, and a CD-ROM with 350 questions in one full-length simulation. Very dense and comprehensive. Useful only if started early, possibly with coursework. Excellent as a reference for studying. Somewhat expensive for the amount of material. The software is also available separately. Books and CD-ROMs can be purchased by calling 1-800-KAP-ITEM.

A⁻***Step-Up: A High-Yield, Systems-Based Review for the USMLE Step 1*****\$34.95**

Review

MEHTA

Lippincott Williams & Wilkins, 2003, 360 pages, ISBN 0781737931

A unique organ system–based review text useful for integrating the basic sciences covered in Step 1. Composed primarily of outlines, charts, tables, and diagrams. The appendix includes 38 clinical cases and an alphabetical section on pharmacology. Contains some errors. The organ system format appeals to many students and serves as a good contrast to other review sources. Includes useful “quick hit” facts.

B⁺***Underground Clinical Vignettes: Step 1 Bundle*****\$143.95**

Review

BHUSHAN

Blackwell Science, 2005, 9 volumes, ISBN 1405104082

All nine volumes of the UCV Step 1 books. Designed for easy quizzing. Case-based vignettes provide a good review supplement. Best if started early with coursework or used in conjunction with another primary review source.

B⁺***Blueprints Step 1 Q&A*****\$28.95**

Test/350 q

CLEMENT

Blackwell Science, 2003, 167 pages, ISBN 140510323X

Contains one full-length exam of 350 questions split into blocks of 50. Written by students. Excellent for practicing the multistep questions that are becoming increasingly prevalent on the real exam. Questions are at times overly specific but overall are high yield.

B⁺***Appleton and Lange's USMLE Step 1 Outline Review*****\$39.95**

Review

GOLDBERG

McGraw-Hill, 2003, 300 pages, ISBN 0071390170

A comprehensive outline review of basic science topics. Includes essential facts, diseases, and disorders. Also offers a bulleted treatment of major abnormal processes by system. Includes black-and-white images of pathology and histology throughout.

B⁺***Rapid Review for USMLE Step 1*****\$34.95**

Review/1400 q

GOLJAN

Mosby, 2002, 314 pages, ISBN 0323008410

Outline format with high-yield marginal notes, figures, and tables that highlight key content. Narrative clinical boxes illustrate clinical relevance. Practice exams provide clinically oriented questions. The CD-ROM includes the questions from the book but is poorly designed without an option to omit already-answered questions from practice sessions. Reviews are mixed regarding the similarity of the content to the actual exam; however, the format is comparable.

B⁺***Lange Q&A for the USMLE Step 1*****\$39.95**

Test/1195 q

KING

McGraw-Hill, 2005, 480 pages, ISBN 0071445781

Features seven subject-based tests and three 100-question comprehensive exams. A good buy for the number of questions. Gives exhaustive explanations of right and wrong answers and offers a reasonable, straightforward, question-based review with which to assess your strengths and weaknesses. Testing includes references to diagrams, images, and a few color plates.

B⁺***NMS Review for USMLE Step 1*****\$42.95**

Test/850 q

LAZO

Lippincott Williams & Wilkins, 2002, 436 pages, ISBN 0781732921

A text that includes a CD-ROM and serves as a good source of practice questions and answers. Some questions are too picky or difficult. Annotated explanations are well written but are sometimes unnecessarily detailed. Organized as 17 practice exams. The six pages of color plates are helpful. The CD-ROM attempts to simulate the CBT format but is disorganized.

B⁺	<p><i>Kaplan's USMLE Step 1 Qbook</i></p> <p>MANLEY</p> <p>Kaplan, 2005, 446 pages, ISBN 0743262387</p> <p>Consists of seventeen 50-question exams organized by the traditional basic science disciplines. Good USMLE-style questions with clear, detailed explanations. Lacks classic images typically seen on the exam. Comparable to the Lange and NMS question reviews.</p>	\$44.95	Test/850 q
B	<p><i>USMLE Step 1 Secrets</i></p> <p>BROWN</p> <p>Elsevier, 2004, 313 pages, ISBN 1560535709</p> <p>Clarifies difficult concepts in a concise, easy-to-read manner. Complements other boards study material in that it helps students understand preclinical fundamentals rather than encouraging the rote memorization of facts. The easy-to-read style allows for rapid review during downtime. The only drawback is its limited breadth.</p>	\$37.95	Review
B	<p><i>Medical Boards—Step 1 Made Ridiculously Simple</i></p> <p>CARL</p> <p>MedMaster, 2003, 367 pages, ISBN 0940780593</p> <p>Quick and easy reading. The table and chart format is organized by subject. Reviews are mixed. Some charts are poorly labeled. Consider as an adjunct. Compare with Yeh's <i>Crashing the Boards: USMLE Step 1</i>.</p>	\$29.95	Review
B	<p><i>Gold Standard Prep Set for USMLE Step 1</i></p> <p>KNOUSE</p> <p>Gold Standard, 2004</p> <p>A set of 48 approximately 90-minute audiotapes covering USMLE Step 1 material. Limited but positive feedback on an updated and expanded set of audiotapes. Used by some students as a way to review while driving, while working out, and during downtime. Contains some inaccuracies. Available only by mail order through the company's Web site, www.boardprep.net.</p>	\$309.00	Audiotapes
B	<p><i>PreTest Clinical Vignettes for the USMLE Step 1</i></p> <p>MCGRAW-HILL</p> <p>McGraw-Hill, 2004, 366 pages, ISBN 0071422918</p> <p>Clinical vignette-style questions with detailed explanations. Organized as eight blocks of 50 questions covering basic sciences. Serves as a good self-evaluation tool, although questions may not mirror those on the actual USMLE exam.</p>	\$24.95	Test/400 q

B***Cracking the Boards: USMLE Step 1*****\$34.95**

Review/400 q

PRINCETON REVIEW

Random House, 2000, 796 pages, ISBN 0375761632

A comprehensive text review based on the USMLE content outline, written by past and present medical students. The style is wordy and broad but offers few details. The organ-based format appeals to some students. Includes many labeled illustrations, charts, and photos.

B***USMLE Step 1 Recall: Buzzwords for the Boards*****\$34.95**

Review

REINHEIMER

Lippincott Williams & Wilkins, 2005, 464 pages, ISBN 0781745136

Quizzes on main topics and key points presented in a two-column question-and-answer format. Good for self-testing, group study, and quick review. Use as a change of pace. Hits many important clinical features but is not comprehensive or tightly organized. Sometimes focuses on obscure details and memorization rather than on the comprehension and integration that the real exam emphasizes.

B***USMLE Step 1 Recall PDA: Buzzwords for the Boards*****\$32.95**

PDA

REINHEIMER

Lippincott Williams & Wilkins, 2001, ISBN 078173343X

The PDA version of the book of the same name. Useful for quick review.

B***Crashing the Boards: USMLE Step 1*****\$27.95**

Review

YEH

Lippincott Williams & Wilkins, 1999, 167 pages, ISBN 0781719771

Brief coverage of high-yield topics. Great diagrams; exhibits a good sense of humor. No photos are included. Good organization (bulleted facts and highlighted boxing); useful for supplementary, last-minute review. Incomplete and outdated book reviews are included in the back. Retains outdated strategies for the paper-and-pencil exam. Compare with Carl's *Medical Boards—Step 1 Made Ridiculously Simple*.

B-***Exam Master Step 1*****\$149.00**

Test/8000 q

EXAM MASTER

Exam Master Corporation, 2001, ISBN 1581290683

Windows/Mac-based testing software with access to up to 8000 Step 1 questions. Questions are relatively simple, but some are obscure. Offers the ability to hide multiple-choice options. The new version eliminates K-type, nonclinical questions and provides compatibility with Windows 98.

B-***Rypins' Basic Sciences Review, Vol. I*****\$39.95**

Review/1000 q

FROHLICH**Lippincott Williams & Wilkins, 2001, 832 pages,
ISBN 0781725186**

A multitopic textbook with few figures and tables. A good general reference, but should be used with other subject-specific sources. Well priced for the number of pages and questions. Requires extensive time commitment. Includes good pathology/pharmacology coverage.

B-***Rypins' Questions and Answers for Basic Sciences Review*****\$34.95**

Test/1600 q

FROHLICH**Lippincott Williams & Wilkins, 2001, 288 pages,
ISBN 0781725208**

Questions with answers to supplement Rypins' Basic Sciences Review. A decent overall question-based review of all subjects. Good-quality questions, but answers lack detail. Requires time commitment. Includes a CD-ROM.

A-**High-Yield Embryology****\$24.95**

Review

DUDEK

Lippincott Williams & Wilkins, 2001, 151 pages,

ISBN 0781721326

A very good, concise review of embryology for the USMLE. Offers excellent organization with clinical correlations. Includes a high-yield list of embryologic origins of tissues. No index or questions.

A-**High-Yield Neuroanatomy****\$24.95**

Review

FIX

Lippincott Williams & Wilkins, 2005, 178 pages,

ISBN 0781758998

A clean, easy-to-read outline format. Offers straightforward text with excellent diagrams and illustrations. The first several chapters are particularly good. Compare with Goldberg's *Clinical Neuroanatomy Made Ridiculously Simple*. No index.

A-**Rapid Review: Gross and Developmental Anatomy****\$31.95**

Review/100 q

MOORE

Mosby, 2002, 220 pages, ISBN 0323012019

A detailed treatment of basic anatomy and embryology, presented in an outline format similar to that of other books in the series. At times more detailed than necessary for boards review. Contains high-yield charts and figures throughout. Two 50-question tests with extensive explanations are included, with additional questions on the CD-ROM. Compare to *High-Yield Anatomy*.

A-**Case Files: Gross Anatomy****\$29.95**

Review

TOY

McGraw-Hill, 2005, 345 pages, ISBN 0071437797

A resource that offers both gross anatomy basics and clinical cases covering several high-yield anatomy topics. Also features a concise discussion of anatomy essentials. Contains few diagrams, but those that are included are high yield.

A ⁻	<p>USMLE Road Map: Gross Anatomy</p> <p>WHITE</p> <p>McGraw-Hill, 2003, 250 pages, ISBN 0071399216</p> <p>An outline treatment of gross anatomy with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter. An especially effective chart format is employed throughout, with clearly labeled illustrations of basic anatomy. Limited student feedback</p>	\$19.95	Review/100 q
A ⁻	<p>USMLE Road Map: Neuroscience</p> <p>WHITE</p> <p>McGraw-Hill, 2004, 210 pages, ISBN 0071422870</p> <p>An outline review of basic anatomy and physiology with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter. Limited student feedback.</p>	\$24.95	Review/80 q
B ⁺	<p>Rapid Review: Histology and Cell Biology</p> <p>BURNS</p> <p>Mosby, 2002, 215 pages, ISBN 0323008348</p> <p>Similar to other books in the series. Features an outline of basic concepts with numerous charts, but histology images are very limited. Two 50-question multiple-choice tests are presented with explanations. The CD-ROM contains additional questions and pathology images. Compare to <i>High-Yield Histology</i>.</p>	\$29.95	Review/100 q
B ⁺	<p>High-Yield Gross Anatomy</p> <p>DUDEK</p> <p>Lippincott Williams & Wilkins, 2002, 190 pages, ISBN 0781730430</p> <p>An excellent, concise review with clinical correlations. Contains well-labeled, high-yield radiologic images. May be useful to supplement with an atlas. No index.</p>	\$24.95	Review
B ⁺	<p>High-Yield Histology</p> <p>DUDEK</p> <p>Lippincott Williams & Wilkins, 2004, 288 pages, ISBN 0781747635</p> <p>A quick and easy review of a relatively low-yield subject. Tables include some high-yield information. Contains good pictures. The appendix features classic electron micrographs.</p>	\$24.95	Review

B⁺	<p><i>Clinical Neuroanatomy Made Ridiculously Simple</i> GOLDBERG MedMaster, 2003, 97 pages, ISBN 0940780461</p> <p>An easy-to-read, memorable, and simplified format with clever hand-drawn diagrams. Offers a quick, high-yield review of clinical neuroanatomy. Good emphasis on clinically relevant pathways, cranial nerves, and neurologic diseases. Includes a CD-ROM that offers CT and MRI images as well as a tutorial on neurologic localization. Compare with Fix's <i>High-Yield Neuroanatomy</i>.</p>	\$19.95	Review/Few q
B⁺	<p><i>BRS Gross Anatomy Flash Cards</i> SWANSON Lippincott Williams & Wilkins, 2005, 254 pages, ISBN 0781756545</p> <p>High-yield anatomy clinical cases presented in flash-card format. Anatomy basics are generally excluded. A useful, boards-relevant resource for students who like to study with flash cards and are reasonably well versed in anatomy.</p>	\$29.95	Flash cards
B⁺	<p><i>Blueprints Notes & Cases: Neuroscience</i> WECHSLER Lippincott Williams & Wilkins, 2004, 228 pages, ISBN 1405103493</p> <p>High-yield cases followed by a discussion and tables, presented in a format similar to that of other books in the <i>Blueprints</i> series. Offers important gross neuroanatomy and neurophysiology facts, but diagrams must be improved if the book is to be considered sufficiently comprehensive for boards review.</p>	\$28.95	Review
B	<p><i>Neuroscience at a Glance</i> BARKER Blackwell Science, 2003, 128 pages, ISBN 1405111240</p> <p>A high-yield treatment of basic principles in neuroscience using figures only, with one topic presented on each page. Includes a highly effective appendix of pathways. Most useful when used with the neuroscience course. Limited student feedback.</p>	\$29.95	Review
B	<p><i>Underground Clinical Vignettes: Anatomy</i> BHUSHAN Lippincott Williams & Wilkins, 2005, 128 pages, ISBN 1405104090</p> <p>Concise clinical cases illustrating approximately 100 frequently tested diseases with an anatomic basis. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.</p>	\$17.95	Review

B	<p><i>Platinum Vignettes: Anatomy and Embryology</i> BROCHERT Elsevier, 2003, 110 pages, ISBN 1560535814 Fifty clinical case scenarios presented in a user-friendly format, with the question appearing on the front of each page and the answer printed on the back. Similar in style to other books in the <i>Platinum Vignettes</i> series; may be of benefit for students who wish to self-quiz. Relatively few cases are presented considering that both anatomy and embryology are covered. Expensive for amount of material.</p>	\$24.95	Review
B	<p><i>BRS Embryology</i> DUDEK Lippincott Williams & Wilkins, 2005, 287 pages, ISBN 0781757266 An outline-based review of embryology that is typical for the <i>BRS</i> series. Offers a good but overly detailed review of important embryology. A discussion of congenital malformations is included at the end of each chapter along with relevant questions. The comprehensive exam at the end of the book is high yield.</p>	\$34.95	Review/500 q
B	<p><i>BRS Neuroanatomy</i> FIX Lippincott Williams & Wilkins, 2002, 457 pages, ISBN 0781728290 An updated text that covers the anatomy and embryology of the nervous system. Complete but lengthy; requires time commitment. Compare with <i>High-Yield Neuroanatomy</i> by the same author.</p>	\$32.95	Review/500 q
B	<p><i>BRS Cell Biology and Histology</i> GARTNER Lippincott Williams & Wilkins, 2003, 352 pages, ISBN 0781733103 An outline format that is useful for looking up cell biology and histology information, presented in a style that is typical of the <i>BRS</i> series. Could be used alone for cell biology review, but not enough histology images to be considered comprehensive. Includes a CD-ROM with questions.</p>	\$32.95	Review/500 q
B	<p><i>Clinical Anatomy Made Ridiculously Simple</i> GOLDBERG MedMaster, 2002, 175 pages, ISBN 0940780534 Easy reading, simple diagrams, and lots of mnemonics and amusing associations. Incomplete. The humorous style has variable appeal to students, so browse before buying. Offers good coverage of selected topics. Best if used during coursework.</p>	\$19.95	Review

B	<p>Netter's Atlas of Human Physiology</p> <p>HANSEN</p> <p>Icon Learning Systems, 2002, 250 pages, ISBN 1929007019</p> <p>An organ system–based text with more than 250 of Dr. Netter's classic illustrations. Offers a clear, concise, “big picture” view of physiology. May be too detailed for boards review. Limited student feedback.</p>	\$39.95	Review
B	<p>PreTest Neuroscience</p> <p>SIEGEL</p> <p>McGraw-Hill, 2005, 322 pages, ISBN 0071436510</p> <p>Similar to other books in the <i>PreTest</i> series. Features a question-and-answer format that is not necessarily in USMLE style. Black-and-white images are referenced to questions throughout. Includes a brief high-yield section. Limited student feedback.</p>	\$24.95	Test/500 q
B	<p>Wheater's Functional Histology</p> <p>YOUNG</p> <p>Elsevier, 2000, 413 pages, ISBN 0443056129</p> <p>A color atlas with pictures of normal histology and accompanying text. Useful as a text for coursework. Skim through the photomicrographs for USMLE review. Image captions provide an excellent source for the review of basic cell biology.</p>	\$64.95	Review
B–	<p>Anatomy Recall</p> <p>BLACKBOURNE</p> <p>Lippincott Williams & Wilkins, 2000, 368 pages, ISBN 0683304364</p> <p>Presented in question-and-answer format. Good for quick review, but may be too detailed for boards review.</p>	\$32.95	Review
B–	<p>BRS Gross Anatomy</p> <p>CHUNG</p> <p>Lippincott Williams & Wilkins, 2005, 530 pages, ISBN 0781753090</p> <p>A detailed, lengthy text in outline format with illustrations and tables. Better for coursework than for quick boards review. Features a good clinical correlation section.</p>	\$32.95	Review/500 q
B–	<p>Essentials of Clinical Neuroanatomy and Neurophysiology</p> <p>GILMAN</p> <p>F. A. Davis, 2003, 281 pages, ISBN 0803607725</p> <p>A well-organized discussion of neuroanatomy, neurophysiology, and neuropharmacology presented with illustrations and images. Too dense for boards review.</p>	\$29.95	Review

B-	<p><i>PreTest Anatomy, Histology, & Cell Biology</i> KLEIN McGraw-Hill, 2005, 526 pages, ISBN 0071437495 Difficult questions with detailed answers as well as some illustrations. Requires extensive time commitment. Includes a high-yield section that highlights clinically relevant relationships and lessons.</p>	\$24.95	Test/500 q
B-	<p><i>Histology and Neural Anatomy: Comprehensive Review in 2000 Multiple-Choice Questions and Answers</i> PAPKA Biotest, Inc., 2004, 427 pages, ISBN 1893720136 A comprehensive outline review. Lacks illustrations and includes a large number of low-quality questions with no explanations, but answers are cross-referenced to the text. Consider using with coursework. Limited student feedback.</p>	\$25.95	Review/2000 q
B-	<p><i>Clinical Anatomy: An Illustrated Review with Questions and Explanations</i> SNELL Lippincott Williams & Wilkins, 2001, 272 pages, ISBN 0781729890 A well-organized summary of Snell's major book. Includes excellent diagrams and tables. Questions incorporate radiographs, CT scans, and MRIs. Does not cover neuroanatomy or embryology. Neither the text nor the questions are as clinical as the title implies. Only some answers have explanations, and most are too short.</p>	\$32.00	Review/500 q
B-	<p><i>Imaging Atlas of Human Anatomy</i> WEIR Elsevier, 2003, 226 pages, ISBN 0723432112 An atlas of diagnostic images for all major systems, including MRIs, CT scans, and brief explanations of diagnostic methods. Useful primarily as an imaging reference for boards review.</p>	\$44.95	Atlas

A***High-Yield Behavioral Science*****\$19.95**

Review

FADEM

Lippincott Williams & Wilkins, 2001, 144 pages,

ISBN 0781730848

A clear, concise, quick review of behavioral science. Offers a logical presentation with cramtable charts, graphs, and tables. Features a short but adequate statistics chapter. No index.

A-***Underground Clinical Vignettes: Behavioral Science*****\$17.95**

Review

BHUSHAN

Lippincott Williams & Wilkins, 2005, 114 pages,

ISBN 1405104104

Concise clinical cases illustrating commonly tested diseases in behavioral science. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other review sources. Although the case diagnoses have been moved to the back of the book, the discussion still reveals the answer on the same page. Some cases lack detail. Twenty questions are included in the back.

A-***BRS Behavioral Science*****\$32.95**

Review/500 q

FADEM

Lippincott Williams & Wilkins, 2005, 292 pages,

ISBN 0781757274

An easy-to-read outline format with boldfacing of key terms. Offers good, detailed coverage of high-yield topics. The text is lengthy and gives more information than may be needed for the USMLE. Includes excellent tables and charts as well as a short but complete statistics chapter. Offers great coverage of ethics and patient communication topics. Also features good review questions, including a 100-question comprehensive exam at the end of the book. The font size of the new edition is significantly smaller than that of previous editions.

A-***Blueprints Notes & Cases: Behavioral Science and Epidemiology*****\$28.95**

Review/184 q

NEUGROSCHI

Lippincott Williams & Wilkins, 2004, 201 pages,
ISBN 1405103558

A case-oriented approach toward behavioral science, presented as part of the *Blueprints Notes & Cases* series. Includes the HPI, a basic science review and discussion, key points, and questions. The 8.5- by 11-inch layout may feel overwhelming to some, but the font size is conducive to easy review. A good way to master the intangibles of behavioral science, but slightly more detailed than warranted for boards review.

A-***Rapid Review: Behavioral Science*****\$32.95**

Review/100 q

STEVENS

Mosby, 2004, 352 pages, ISBN 0323020070

A quick outline format covering basic topics in behavioral science, human development, and biostatistics, presented in a format similar to that of other books in the *Rapid Review* series. Two 50-question multiple-choice tests are included with explanations. Somewhat more detailed on specific disorders, but not sufficient as a sole biostatistics review. The CD-ROM contains additional questions. Compare with *High-Yield Behavioral Science*. Limited student feedback.

B+***Platinum Vignettes Series: Behavioral Science*****\$24.95**

Review

BROCHERT

Elsevier, 2003, 106 pages, ISBN 1560535768

A series of cases followed by explanations and discussions on the following page, presented in a format similar to that of other books in the *Platinum Vignettes* series. In contrast to the *Underground Clinical Vignettes*, the *Platinum* series includes vignettes for biostatistics; however, there are only half as many cases. Expensive for the amount of material.

B+***High-Yield Biostatistics*****\$24.95**

Review

GLASER

Lippincott Williams & Wilkins, 2005, 104 pages,
ISBN 078179644X

A well-written text, but some explanations are confusing. Offers extensive coverage for a low-yield topic. Includes good review questions and tables. For the motivated student; not for last-minute cramming. Suitable as a course companion. Best used in conjunction with a behavioral science resource.

B⁺***USMLE Behavioral Science Made Ridiculously Simple*****\$16.95**

Review

SIERLES

MedMaster, 1998, 171 pages, ISBN 0940780348

Easy reading, and reasonably high yield for the amount of text. Includes medical sociology; strong on psychopathology with illustrative examples. No biostatistics. Sometimes offers too much detail on low-yield topics.

B***Behavioral Sciences and Outpatient Medicine for the Boards and Wards*****\$19.95**

Review

AYALA

Lippincott Williams & Wilkins, 2001, 100 pages,
ISBN 0632045787

Presented in a clear and informative format similar to that of other books in the *Boards and Wards* series. Covers some low-yield topics.

B⁻***PreTest Behavioral Science*****\$24.95**

Test/500 q

EBERT

McGraw-Hill, 2002, 358 pages, ISBN 0071374701

Contains detailed answers cross-referenced with other resources. Good test questions. Requires time commitment. Includes a brief high-yield section.

A⁻***Underground Clinical Vignettes: Biochemistry*****\$17.95**

Review

BHUSHAN

Lippincott Williams & Wilkins, 2005, 113 pages,
ISBN 1405104112

Concise clinical cases illustrating approximately 100 frequently tested diseases with a biochemical basis. Cardinal signs, symptoms, and buzzwords are highlighted. A useful supplement to other sources of review.

A⁻***Lippincott's Illustrated Reviews: Biochemistry*****\$44.95**

Review/250 q

CHAMPE

Lippincott Williams & Wilkins, 2005, 534 pages,
ISBN 0781722659

An excellent book that offers good clinical correlations as well as highly effective color diagrams. Offers a comprehensive review of biochemistry, including some low-yield topics. The new edition also includes high-yield chapter summaries and a “big picture” chapter at the end of the book that highlights the most important concepts. Requires time commitment; skim high-yield diagrams to maximize USMLE review. Best used with coursework.

A⁻***Rapid Review: Biochemistry*****\$31.95**

Review/100 q

PALLEY

Mosby, 2003, 320 pages, ISBN 0323008356

A quick outline format covering basic topics in biochemistry, presented in a format similar to that of other books in the *Rapid Review* series. High-yield disease correlation boxes are useful for review. Excellent tables and high-yield figures are featured throughout. Also includes two 50-question multiple-choice tests with explanations plus a CD-ROM with additional questions. Compare to *High-Yield Biochemistry*.

B⁺***High-Yield Biochemistry*****\$24.95**

Review

WILCOX

Lippincott Williams & Wilkins, 2003, 128 pages,
ISBN 0781743141

A concise and crammable text in outline format with good clinical correlations at the end of each chapter. Features many diagrams and tables. Good as a study supplement.

B***High-Yield Cell and Molecular Biology*****\$24.95**

Review

DUDEK

Lippincott Williams & Wilkins, 1999, 128 pages,
ISBN 0683303597

Cellular and molecular biology presented in an outline format, with good diagrams and clinical correlations. Brief but complete. Includes descriptions of laboratory techniques and genetic disorders. No questions or vignettes.

B***Clinical Biochemistry*****\$36.95**

Review

GAW

Churchill Livingstone, 1999, 176 pages, ISBN 0443061831

Biochemistry and physiology presented in a clinical framework. Visually pleasing. Focuses on adult medicine; skimpy on inherited disorders, genetics, and molecular biochemistry. Case studies are included throughout, but no standard question-and-answer exercises are given. May be more wards than boards oriented.

B***Clinical Biochemistry Made Ridiculously Simple*****\$22.95**

Review

GOLDBERG

MedMaster, 1999, 95 pages, ISBN 0940780305

A conceptual approach toward clinical biochemistry, presented with humor. The casual style does not appeal to all students. Mnemonics tend to be somewhat complicated. Offers a good overview and integration of all metabolic pathways. Includes a 23-page clinical review that is very high yield and crammable. Also contains a unique foldout “road map” of metabolism. For students with a firm biochemistry background.

B***PreTest Biochemistry & Genetics*****\$24.95**

Test/500 q

INGRAM-SMITH

McGraw-Hill, 2005, 384 pages, ISBN 0071437479

Difficult questions with detailed, referenced explanations. Best for the motivated student who uses it along with a review book. Contains some questions on biochemical disorders and metabolism but no clinical vignettes. Features six pages of high-yield facts focusing on genetically based diseases.

B***STARS Biochemistry Review*****\$27.50**

Review/600 q

ROSKOSKI

W. B. Saunders, 1996, 242 pages, ISBN 0721651755

A content review in dense outline format with small type. Chapters are short and include only relevant pathways. Good for students who prefer an outline-based review. Parallels the core text by the same authors. A comprehensive exam at the end of the book has some questions with a clinical slant.

B***Metabolism at a Glance*****\$34.95**

Review

SALWAY

Blackwell Science, 2004, 128 pages, ISBN 1405107162

A concise and impressive review of the biochemical pathways involved in metabolism. Intricate figures depict the interplay between the various reactions. Beyond the scope of the USMLE, but a unique resource nonetheless.

B***Case Files: Biochemistry*****\$29.95**

Review

TOY

McGraw-Hill, 2005, 414 pages, ISBN 0071437819

A text that is divided into clinical cases followed by clinical correlations, a discussion, and take-home pearls, presented in a format similar to others in the *Case Files* series. A few questions accompany each case. The black-and-white figures are sometimes too small to read, but the clinical correlations make biochemistry concepts easier to remember. Too lengthy for rapid review; best for students who enjoys problem-based learning.

A

Clinical Microbiology Made Ridiculously Simple

\$25.95

Review

GLADWIN

MedMaster, 2003, 272 pages, ISBN 0940780496

A very good chart-based review of microbiology that includes clever and humorous mnemonics. The best of this series. The text is easy to read, and an excellent antibiotic review helps for pharmacology as well. The style of the series does not appeal to everyone. Requires a supplemental source for immunology. Excellent if you have limited time or are “burning out.”

A

Rapid Review: Microbiology and Immunology

\$32.95

Review/100 q

ROSENTHAL

Mosby, 2002, 395 pages, ISBN 0323008402

Similar to other books in the *Rapid Review* series. Contains a significant number of excellent tables and figures. Two 50-question tests with extensive explanations complement the topics covered in the review. The CD-ROM contains additional questions, but their format is poor. Overall, one of the best in the *Rapid Review* series.

A-

Basic Immunology

\$54.95

Review

ABBAS

Elsevier, 2004, 322 pages, ISBN 1416024034

A text that includes colorful diagrams, pictures, and tables that students will find useful for quick review. Also offers abundant text as well as a lengthy glossary for those who wish to delve into the topic further for the boards. Features online access to the same text.

A-

Underground Clinical Vignettes: Microbiology Vols. I & II

\$17.95 ea.

Review

BHUSHAN

Lippincott Williams & Wilkins

Microbiology, Vol. I: 2005, 112 pages, ISBN 1495194129

Microbiology, Vol. II: 2005, 134 pages, ISBN 1405104139

Concise clinical cases illustrating frequently tested diseases in microbiology and immunology (approximately 100 cases per volume). Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.

A-***Microcards*****\$28.98**

Flash cards

HARPAVAT**Lippincott Williams & Wilkins, 2002, 380 pages,
ISBN 0781722004**

A very useful resource for students who like to use flash cards for review. Some cards include excellent flow charts of important classes of bacteria or viruses. Most of the other cards include the bacterium or virus, clinical presentation, pathobiology, diagnosis, treatment, and important quick facts.

A-***High-Yield Immunology*****\$19.95**

Review

JOHNSON**Lippincott Williams & Wilkins, 1999, 68 pages, ISBN 0683306146**

Presented in a format typical of the *High-Yield* series. Accurately covers high-yield details within the topic in proportion to boards coverage of immunology. Good for quick review. Some illustrations and diagrams could be improved, and some sections may not be detailed enough.

A-***Medical Microbiology and Immunology: Examination and Board Review*****\$39.95**

Review/654 q

LEVINSON**McGraw-Hill, 2002, 614 pages, ISBN 0071382178**

Clear, concise writing with excellent diagrams and tables. Includes an excellent immunology section. The "Summary of Medically Important Organisms" is highly cramable. Requires time commitment. Can be detailed and dense; best if started early with the course. Covers all topics, including some that are low yield. Includes good practice questions and a comprehensive exam, but questions have letter answers only. Compare with *Lippincott's Illustrated Reviews: Microbiology*.

B+***Concise Medical Immunology*****\$36.95**

Review

DOAN**Lippincott Williams & Wilkins, 2005, 267 pages,
ISBN 078175741X**

A concise text with useful diagrams, illustrations, and tables. Good for students who need extra immunology review or wish to study the subject thoroughly for the boards. End-of-chapter multiple-choice questions help reinforce key concepts.

B⁺	<p><i>Case Studies in Immunology: Clinical Companion</i> ROSEN Garland Science, 2001, 250 pages, ISBN 0815340508 Originally designed as a clinical companion to Janeway's <i>Immunobiology</i>, this text provides an excellent synopsis of the major disorders of immunity in a clinical vignette format. Integrates basic and clinical science. Excellent images, illustrations, questions, and discussion.</p>	\$33.95	Review/100 q
B⁺	<p><i>How the Immune System Works</i> SOMPAYRAC Blackwell Science, 2002, 144 pages, ISBN 063204702X A concise overview of immunology that attempts to simplify complicated concepts. Includes a good general introduction, but best used as a companion to other, more detailed resources. Weak in clinical immunology. Limited student feedback.</p>	\$24.95	Review
B⁺	<p><i>Case Files: Microbiology</i> TOY McGraw-Hill, 2005, 389 pages, ISBN 0071445749 Fifty clinical microbiology cases reviewed in an interactive learning format. Each case is followed by a clinical correlation, a discussion with boldfaced buzzwords, and questions. Cases are useful for boards review, since key ideas can be readily associated with the appropriate clinical scenario.</p>	\$29.95	Review
B⁺	<p><i>Clinical Microbiology Review</i> WARINNER Wysteria, 2001, 152 pages, ISBN 0967783933 A concise yet comprehensive review in chart format with some clinical correlations. Each page is devoted to a single organism with ample space for adding notes during class. Contains no immunology. Spatial organization, color coding, and bulleting of facts facilitate subject review. A great cross-reference section groups organisms by general characteristics. The new edition includes color plates of significant microbes. Limited but positive student feedback. Compare with Topf's <i>Microbiology Companion</i>.</p>	\$36.95	Review

B ⁺	<p><i>Appleton & Lange Outline Review: Microbiology and Immunology</i> YOTIS McGraw-Hill/Appleton & Lange, 2004, 200 pages, ISBN 0071405666</p> <p>A well-organized approach toward the microbiology section of the boards, addressing all areas included in the exam. Lacks detailed treatment of autoimmune disorders, but an excellent resource to use in addition to class notes. A good resource for organization of the material. Its sparse use of images could be a drawback.</p>	\$29.95	Review
B ⁺	<p><i>Appleton & Lange's Review of Microbiology & Immunology</i> YOTIS McGraw-Hill, 2001, 288 pages, ISBN 0071362657</p> <p>A large number of questions with detailed answers. Inadequate as a primary source, but a good supplement for the motivated student. Well referenced with effective diagrams, figures, and tables. Includes a good immunology section but weak coverage of immune disorders.</p>	\$34.95	Test/995 q
B	<p><i>Immunology for the Boards and Wards</i> AYALA Blackwell Science, 2001, 72 pages, ISBN 0632045744</p> <p>Similar in style to other books in the <i>Boards and Wards</i> series. Not specifically tailored to USMLE material, but includes many high-yield tables. Contains approximately 20 questions throughout the text. No illustrations. Limited student feedback.</p>	\$19.95	Review/19 q
B	<p><i>Microbiology and Immunology for the Boards and Wards</i> AYALA Lippincott Williams & Wilkins, 2005, 233 pages, ISBN 1405104686</p> <p>An outline format that may be appealing to some students but overwhelming for others. Includes some figures and tables for those who do not favor the format. A microbiology and immunology review is also included along with a comprehensive assessment.</p>	\$24.95	Review
B	<p><i>Blueprints Notes & Cases: Microbiology and Immunology</i> GANDHI Lippincott Williams & Wilkins, 2004, 208 pages, ISBN 1405103477</p> <p>Fifty-eight succinct clinical cases covering boards-relevant microbiology and immunology facts. Charts, tables, illustrations, and useful “thumbnails” are included in the discussion section to facilitate rapid synthesis of key concepts. Best used during microbiology coursework so that it can be readily reviewed for the boards. For students proficient in immunology.</p>	\$28.95	Review

B***BRS Microbiology and Immunology*****\$32.95**

Review/500 q

JOHNSON

Lippincott Williams & Wilkins, 2001, 300 pages,
ISBN 0781727707

A concise outline format with good questions and illustrations. The immunology section is especially useful. For the motivated student.

B***Bugcards: The Complete Microbiology Review for Class, the Boards, and the Wards*****\$26.50**

Flash cards

LEVINE

BL Publishing, 1998, 154 pages, ISBN 0967165504

High-quality flash cards (similar to “Pharm Cards”) designed for rapid class and USMLE microbiology review. Cards cover all medically relevant bacteria, viruses, fungi, and parasites and include important buzzwords, mnemonics, and clinical vignettes to aid in recall. Unique “disease process cards” summarize all organisms for a particular disease (e.g., UTI, pneumonia). Useful for a quick review of facts, but not recommended as a comprehensive primary review source.

B***Instant Notes in Immunology*****\$31.95**

Review/125 q

LYDYARD

Garland Science, 2004, 322 pages, ISBN 1859960391

A comprehensive review of immunology with effective figures throughout. Well organized, but too detailed for boards review. Best used with the course. Questions are not in current USMLE format and do not include explanations. High-yield tables of principal cytokines and selected molecules are included. Limited student feedback.

B***Lippincott's Illustrated Reviews: Microbiology*****\$35.95**

Review/Few q

STROHL

Lippincott Williams & Wilkins, 2001, 528 pages,
ISBN 0397515685A comprehensive, highly illustrated review of microbiology similar in style to Champe's *Lippincott's Illustrated Reviews: Biochemistry*. Includes a 50-page color section with more than 150 clinical and laboratory photographs. Compare with Levinson's *Medical Microbiology and Immunology*.**B*****BRS Micro Flash Cards*****\$27.95**

Flash cards

SWANSON

Lippincott Williams & Wilkins, 2003, 250 pages,
ISBN 078174427X

A series of flash cards featuring questions with answers on the reverse side. Useful for students who enjoy an active style of review.

B	<p><i>STARS Microbiology</i> WALKER Elsevier, 1998, 513 pages, ISBN 0721646417 Presents pathogens in a consistent outline format, from pathogenicity to treatment. Features numerous multicolor tables and illustrations. No questions. Requires time commitment. Consider as a course supplement.</p>	\$32.00	Review
B-	<p><i>Microbiology for the Boards and Wards</i> AYALA Blackwell Science, 2001, 163 pages, ISBN 0632045760 A concise review of major and exotic pathogens in a useful outline format. Easy to read. Limited student feedback.</p>	\$18.95	Review/22 q
B-	<p><i>Platinum Vignettes Series: Microbiology</i> BROCHERT Elsevier, 2003, 114 pages, ISBN 1560535741 Fifty clinical case scenarios presented in a unique format, with the case question appearing on the front of the page and the answer printed on the back. May be useful for students who wish to self-quiz. Expensive for the amount of material.</p>	\$24.95	Review
B-	<p><i>PreTest Microbiology</i> KETTERING McGraw-Hill, 2005, 310 pages, ISBN 0071437487 Mixed-quality questions with detailed, sometimes verbose explanations. Useful for additional question-based review in bacteriology and virology, but not high yield. Includes three pages of high-yield facts.</p>	\$24.95	Test/500 q
B-	<p><i>Flash Micro</i> TING Stanford Ink, 1999, 131 pages, ISBN 0967231809 Concise flash cards designed for boards review. Include 190 pathogens but no immunology. Color coded. Compare with Orlando's <i>Medical Micro-Cards</i>. Mixed student feedback.</p>	\$27.95	Flash cards

A***BRS Pathology*****\$32.95**

Review/500 q

SCHNEIDER

Lippincott Williams & Wilkins, 2001, 488 pages,

ISBN 0683302655

An excellent, concise review with appropriate content emphasis. Features outline-format chapters with boldfacing of key facts. Includes good questions with explanations at the end of each chapter and a comprehensive exam at the end of the book. Offers well-organized tables and diagrams as well as some good black-and-white photographs representative of classic pathology that can be correlated with color photographs from an atlas. Also contains a chapter on laboratory testing and “key associations” with each disease. Short on clinical details for vignette questions. Worth the time investment. Most effective if started early and then reviewed during study periods.

A-***Pathophysiology for the Boards and Wards—USMLE Step 1*****\$32.95**

Review/75 q

AYALA

Blackwell Science, 2003, 352 pages, ISBN 1405103426

A system-based outline with a focus on pathology. Well organized with glossy color plates of relevant pathology and excellent, concise tables. The appendix includes a helpful overview of neurology, immunology, “zebras,” syndromes, and pearls.

A-***Lange Flash Cards: Pathology*****\$29.95**

Flash cards

BARON

McGraw-Hill, 2004, 296 pages, ISBN 0071436901

Pathology cards organized with information on one disease per card. Includes pathophysiology, clinical manifestations, treatment, and clinical vignette. Most effective when used at the beginning of the second year through Step 1 preparation. A useful resource with which to organize the breadth of pathology topics covered on the USMLE. Limited student feedback.

A-***Underground Clinical Vignettes: Pathophysiology, Vols. I, II, & III*****\$17.95 each** Review

BHUSHAN

Lippincott Williams & Wilkins

Pathophysiology, Vol. I: 2005, 116 pages, ISBN 1405104147

Pathophysiology, Vol. II: 2005, 114 pages, ISBN 1405104155

Pathophysiology, Vol. III: 2005, 115 pages, ISBN 1405104163

Concise clinical cases illustrating approximately 100 frequently tested pathology and physiology cases in each book. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.

A⁻	<p><i>Pathology Recall</i> CHABRA Lippincott Williams & Wilkins, 2002, 624 pages, ISBN 0781734061</p> <p>A quiz-based text featuring thousands of brief questions. Not in USMLE format. Similar to others in the <i>Recall</i> series. Beyond the scope of Step 1, but an entertaining break from other reviews.</p>	\$32.95	Review
B⁺	<p><i>PreTest Pathology</i> BROWN McGraw-Hill, 2005, 577 pages, ISBN 0071436774</p> <p>Picky, difficult questions with detailed, complete answers. Questions are often obscure or esoteric. Features high-quality black-and-white photographs but no color illustrations. Can be used as a supplement to other review books. For the motivated student. Thirty-five pages of high-yield facts are useful for concept summaries.</p>	\$24.95	Test/500 q
B⁺	<p><i>BrainChip for Pathology</i> GARCIA Blackwell Science, 2002, 144 pages, ISBN 0632046392</p> <p>More than 160 clinical cases and color photographs. Excellent pictures and relevant text.</p>	\$19.95	Review
B⁺	<p><i>Rapid Review: Pathology</i> GOLJAN Mosby, 2004, 463 pages, ISBN 0323023932</p> <p>Similar to other books in the <i>Rapid Review</i> series. Addresses key concepts in pathology in a bulleted outline format with many tables and figures. High-yield marginal notes are useful, but the text can appear cluttered at times. The CD-ROM contains additional questions, but they are not in boards format. Limited student feedback.</p>	\$32.95	Review/100 q
B⁺	<p><i>Pathophysiology of Disease: Introduction to Clinical Medicine</i> McPHEE McGraw-Hill, 2000, 662 pages, ISBN 0838581609</p> <p>An interdisciplinary course text useful for understanding the pathophysiology of clinical symptoms. Effectively integrates the basic sciences with mechanisms of disease. Features great graphs, diagrams, and tables. Most helpful if used during coursework owing to its length. Few non-boards-style questions. The text's clinical emphasis nicely complements <i>BRS Pathology</i>.</p>	\$44.95	Review/Few q

B⁺	<p><i>PreTest Pathophysiology</i> \$24.95 Test/500 q</p> <p>MUFSON McGraw-Hill, 2005, 272 pages, ISBN 0071434925 Includes 500 questions and answers with detailed explanations. Questions may be more difficult than those on the boards. Features a brief section of high-yield topics.</p>
B⁺	<p><i>Pocket Companion to Robbins Pathologic Basis of Disease</i> \$34.95 Review</p> <p>ROBBINS W. B. Saunders, 1999, 800 pages, ISBN 0721678599 Good for reviewing associations between keywords and specific diseases. Highly condensed, complete, and easy to understand. Explains most important diseases and pathologic processes. No photographs or illustrations. Useful as a quick reference.</p>
B	<p><i>Platinum Vignettes Series Pathology I & II</i> \$24.95 each Review</p> <p>BROCHERT Elsevier, 2003, 118 pages, ISBN 1560535695 104 pages, ISBN 1560535725 A text consisting of vignettes that are very similar in style to those of the <i>Underground Clinical Vignette</i> series. However, each volume contains 50 cases for a total of 100, whereas the UCVs offer 300 cases split over three volumes. Overall, offers less bang for the buck than the UCVs.</p>
B	<p><i>Appleton & Lange's Review of General Pathology</i> \$34.95 Test/1300 q</p> <p>CATALANO McGraw-Hill, 2003, 352 pages, ISBN 0071389954 Short text sections followed by numerous questions with answers. Some useful high-yield tables are included at the beginning of each section. Features good photomicrographs. Covers both general and organ-based pathology. Can be used as a supplement to more detailed texts. A good review when time is short.</p>
B	<p><i>Colour Atlas of Anatomical Pathology</i> \$65.95 Review</p> <p>COOKE Churchill Livingstone, 2004, 300 pages, ISBN 0443073600 An impressive photographic atlas of gross pathology. Offers easy-to-read, clinically relevant content.</p>

B***Lange Smart Charts*****\$24.95**

Review

GROYSMAN

McGraw-Hill, 2001, 356 pages, ISBN 0838581757

A flip chart of tables with information grouped together for ease of recall. Organized by body system with mnemonics. Best used as a summary reference for fast review.

B***Robbins Review of Pathology*****\$39.95**

Review/1100 q

KLATT

Elsevier, 2005, 419 pages, ISBN 0721601944

A question book of pathology with answer explanations. Questions are almost all clinically based and are accompanied by a number of high-quality histologic and gross images as well as by references to the Robbins *Pathologic Basis of Disease* and *Basic Pathology* textbooks. Questions are more difficult and detailed than those on the actual exam. Answer explanations are brief but well written. Good to use as a companion to pathology coursework.

B***Pathophysiology of Heart Disease*****\$34.95**

Review

LILLY

Lippincott Williams & Wilkins, 2002, 448 pages,
ISBN 0781740274

A collaborative project by medical students and faculty at Harvard. Well organized, easy to read, and concise; offers comprehensive coverage of cardiovascular pathophysiology from the medical student's perspective. Serves as an excellent bridge between the basic and clinical sciences. Very good for review of this subject, but does not cover other areas of pathology tested on the boards. May be too detailed for boards review.

B***Pathcards*****\$32.95**

Flash cards

MARCUCCI

Lippincott Williams & Wilkins, 2003, 520 cards,
ISBN 0781743990

Presents comprehensive and detailed information in flash-card format rather than attempting to condense boards-relevant material into just one fact per disease state. Appropriate to the level of depth with which pathology is tested on the USMLE, but cards look cramped and are difficult to flip through for rapid review.

B	<p><i>PreTest Physical Diagnosis</i> RETEGUIZ McGraw-Hill, 2003, 382 pages, ISBN 0071411402</p> <p>A collection of clinical vignettes organized by body system, presented in a style similar to that of other books in the <i>PreTest</i> series. May be beyond the scope of Step 1, but could also be used in the clinical years of medical school. Limited student feedback.</p>	\$24.95	Test/500 q
B	<p><i>Renal Pathophysiology: The Essentials</i> ROSE Lippincott Williams & Wilkins, 1994, 351 pages, ISBN 0683073540</p> <p>An excellent review with explanations of various disease processes of the kidney. Includes review questions within the text that are intended for comprehension and are not written in boards style. Would serve as a good reference during boards review.</p>	\$28.00	Review
B	<p><i>Color Atlas of Pathophysiology</i> SILBERNAGL Thieme, 2000, 380 pages, ISBN 0865778663</p> <p>A text containing more than 180 high-quality illustrations demonstrating disturbed physiologic processes that lead to dysfunction. Limited student feedback.</p>	\$39.00	Review
B	<p><i>BRS Pathology Flash Cards</i> SWANSON Lippincott Williams & Wilkins, 2002, 250 cards, ISBN 0781737109</p> <p>A series of 250 pathology flash cards categorized by organ system. Effective when used with the <i>BRS Pathology</i> textbook, but not comprehensive enough when used alone. Most cards have only one high-yield fact.</p>	\$29.95	Flash cards
B-	<p><i>Rypins' Intensive Reviews: Pathology</i> DAMJANOV Lippincott Williams & Wilkins, 1998, 432 pages, ISBN 0397515553</p> <p>Typical of this series. Includes a comprehensive exam with answers and explanations. Illustrated with simple diagrams; no photos are included.</p>	\$21.95	Review/220 q

B-**Review Questions for Human Pathology****\$19.95**

Test/1300 q

JONES

Parthenon, 1999, 322 pages, ISBN 1850705992

Features more than 1300 questions with answers and discussions. Many questions are in outdated USMLE format. Step 1-level questions are interspersed with questions at the level of Step 2 and Step 3. A good value for the price.

B-**Blueprints Notes & Cases Pathophysiology:
Cardiovascular, Endocrine, and Reproduction****\$28.95 each** Review

LEUNG

Lippincott Williams & Wilkins, 2004, 187 pages,
ISBN 1405103507**Blueprints Notes & Cases Pathophysiology: Pulmonary,
Gastrointestinal, and Rheumatology**

FILBIN

Lippincott Williams & Wilkins, 2004, 172 pages,
ISBN 1405103515**Blueprints Notes & Cases Pathophysiology: Renal,
Hematology, and Oncology**

CAUGHEY

Lippincott Williams & Wilkins, 2004, 192 pages,
ISBN 1405103523

These books follow the format of the larger *Blueprints* series, in which each case takes the form of a discussion followed by key points and a series of questions. The pathophysiology volumes would serve a good companion to organ-based teaching modules, but the material is neither comprehensive enough nor sufficiently concise to be high yield for intensive boards preparation.

A⁻***Lippincott's Illustrated Reviews: Pharmacology*****\$44.95**

Review/125 q

HOWLAND

Lippincott Williams & Wilkins, 2006, 552 pages,

ISBN 0781741181

An outline format with practice questions and many excellent illustrations and tables. Cross-referenced to other books in the *Lippincott's Illustrated Reviews* series. Good for the “big picture,” and takes an effective pathophysiologic approach. Highly detailed, so use with coursework and review for the USMLE. For the motivated student.

A⁻***Katzung and Trevor's Pharmacology: Examination and Board Review*****\$39.95**

Review/1000 q

TREVOR

McGraw-Hill, 2005, 645 pages, ISBN 0071422900

A well-organized text in narrative format with concise explanations. Features good charts and tables. Good for drug interactions and toxicities. Offers two practice exams with questions and detailed answers. Includes some low-yield/obscure drugs. The crammable list of “top boards drugs” is especially high yield. Compare closely with *Lippincott's Illustrated Reviews: Pharmacology*.

B⁺***Pharmacology for the Boards and Wards*****\$25.95**

Review/150 q

AYALA

Blackwell Science, 2003, 220 pages, ISBN 1405103248

Like other books in the *Boards and Wards* series, the pharmacology volume is presented primarily in tabular format with bulleted key points. Review questions are in USMLE style. At times can be too dense.

B⁺***Pharm Cards: A Review for Medical Students*****\$32.95**

Flash cards

JOHANNSEN

Lippincott Williams & Wilkins, 2002, 228 pages,

ISBN 0781734010

The updated edition highlights important features of major drugs and drug classes. Good for class review; also offers a quick, focused review for the USMLE. Lacks pharmacokinetics, but features good charts and diagrams. Well liked by students who enjoy flash card-based review. Bulky to carry around.

B⁺	<p><i>BRS Pharmacology Flash Cards</i> KIM Lippincott Williams & Wilkins, 2004, 508 pages, ISBN 0781747961</p> <p>Cards focus on facilitating the recall of drugs used for particular diseases rather than describing these drugs in detail. May be useful for those who find Pharm Cards overwhelming. Considered by many to be an excellent resource for quick review before the boards.</p>	\$27.95	Flash cards
B⁺	<p><i>Lange Smart Charts: Pharmacology</i> PELLETIER McGraw-Hill/Appleton & Lange, 2003, 386 pages, ISBN 0071388788</p> <p>Pharmacology concepts organized into a tabular format. Most useful when used as a secondary source for organization when reviewing material. Limited student feedback.</p>	\$34.95	Review
B⁺	<p><i>Pharm Recall</i> RAMACHANDRAN Lippincott Williams & Wilkins, 1999, 512 pages, ISBN 068330285X</p> <p>An approach toward pharmacology review presented in a question-and-answer “recall” format. Includes a high-yield drug summary. Good for cramming and memorization.</p>	\$32.95	Review
B	<p><i>Underground Clinical Vignettes: Pharmacology</i> BHUSHAN Lippincott Williams & Wilkins, 2005, 129 pages, ISBN 1405104171</p> <p>Concise clinical cases illustrating approximately 100 frequently tested pharmacology concepts. Cardinal signs, symptoms, and buzzwords are highlighted. The clinical vignette style is less effective for pharmacology. Use as a supplement to other sources of review.</p>	\$17.95	Review
B	<p><i>Clinical Pharmacology Made Ridiculously Simple</i> OLSON MedMaster, 2001, 164 pages, ISBN 094078050X</p> <p>Includes general principles and many drug summary charts. Particularly strong in cardiovascular drugs and antimicrobials; incomplete in other areas. Consists primarily of tables; lacks the humorous illustrations and mnemonics typical of this series. Well organized, but occasionally too detailed. Effective as a chart-based review book but not as a sole study source. Must be supplemented with a more detailed text.</p>	\$20.95	Review

B	<p><i>Rapid Review: Pharmacology</i> PAZDERNICK Elsevier, 2005, 316 pages, ISBN 0323008380 Similar to other books in the series. Figures are sparse but are high yield when included. Provides limited detail on mechanisms of action. Contains two 50-question tests with additional questions on a CD-ROM. Compare with <i>High-Yield Pharmacology</i>. Limited student feedback.</p>	\$31.95	Review/100 q
B	<p><i>Instant Pharmacology</i> SAEB-PARSY John Wiley & Sons, 1999, 349 pages, ISBN 0471976393 A text divided into several parts, the first addressing basic mechanisms found in pharmacology. Drugs encountered in this section are summarized in the "Dictionary of Drugs." Concludes with a comprehensive exam. Includes answers but no explanations.</p>	\$39.99	Review/130 q
B	<p><i>PreTest Pharmacology</i> SHLAFER McGraw-Hill, 2005, 379 pages, ISBN 007143688X A text that represents a significant improvement over previous editions of <i>PreTest Pharmacology</i>. A good resource to use after other sources of questions have been exhausted.</p>	\$24.95	Test/500 q
B	<p><i>Case Files: Pharmacology</i> TOY McGraw-Hill, 2005, 420 pages, ISBN 0071445730 A clinical case review book consisting of 52 cases along with useful tables. The text may appeal to students who prefer problem-based learning, but some may find it difficult to review pharmacology using a clinical vignette format.</p>	\$29.95	Review
B-	<p><i>High-Yield Pharmacology</i> CHRIST Lippincott Williams & Wilkins, 2003, 144 pages, ISBN 0781745128 A pharmacology review presented in an easy-to-follow outline format. Contains no questions or index. Offers a good summary. Best used with a more extensive text.</p>	\$24.95	Review

B-***Appleton & Lange's Review of Pharmacology*****\$34.95**

700+ q

KRZANOWSKI

McGraw-Hill, 2004, 156 pages, ISBN 0071377433

A text that contains ample, up-to-date questions along with a 50-question practice test. Best for students who need additional pharmacology questions for boards review. Answers have no accompanying text or explanations, which may pose a challenge for those who require more detailed information.

A***BRS Physiology*****\$32.95**

Review/400 q

COSTANZO

Lippincott Williams & Wilkins, 2003, 352 pages,

ISBN 0781739195

A clear, concise review of physiology that is both comprehensive and efficient, making for fast, easy reading. Includes great charts and tables. Good practice questions are given along with explanations and a clinically oriented final exam. An excellent review book, but may not be enough for in-depth coursework. Respiratory and acid-base sections are comparatively weak.

A***Physiology*****\$44.95**

Review

COSTANZO

Elsevier, 2002, 451 pages, ISBN 1416023275

Comprehensive coverage of concepts outlined in *BRS Physiology*. Offers excellent diagrams and charts. Each systems-based chapter includes a detailed summary of objectives and a boards-relevant clinical case. The new edition also includes online interactive extras. Requires time commitment.

A-***BRS Physiology Cases and Problems*****\$34.95**

Review/Many q

COSTANZO

Lippincott Williams & Wilkins, 2006, 384 pages,

ISBN 078176078X

Roughly 50 cases in vignette format with several questions per case. Includes detailed answers with explanations. For the motivated student.

A-***USMLE Road Map: Physiology*****\$19.95**

Review/50 q

PASLEY

McGraw-Hill, 2003, 216 pages, ISBN 0071400761

A text in outline format incorporating high-yield illustrations. Provides a concise approach to physiology. Clinical correlations are referenced to the text. Questions build on basic concepts and include detailed explanations. Limited student feedback.

B⁺	<p><i>High-Yield Acid Base</i> LONGENECKER Lippincott Williams & Wilkins, 1998, 100 pages, ISBN 0683303937</p> <p>A concise and well-written description of acid-base disorders. Includes chapters discussing differential diagnoses and 12 clinical cases. Introduces a multistep approach to the material. A bookmark with useful factoids is included with the text. No index or questions.</p>	\$18.95	Review
B⁺	<p><i>Appleton & Lange's Review of Physiology</i> PENNEY McGraw-Hill, 2004, 278 pages, ISBN 0071377263</p> <p>Boards-style questions divided into subcategories under physiology. Good if subject-specific questions are desired, but may be too detailed for many students. Some diagrams are used to explain answers. A good way for students to test their knowledge after coursework.</p>	\$34.95	Test/700 q
B⁺	<p><i>Respiratory Physiology: The Essentials</i> WEST Lippincott Williams & Wilkins, 1999, 192 pages, ISBN 0683307347</p> <p>Comprehensive coverage of respiratory physiology. Clearly organized with useful charts and diagrams. The new edition includes appendices with more than 100 questions and answers with explanations. Best used as a course supplement. Limited student feedback.</p>	\$31.00	Review/100 q
B	<p><i>Color Atlas of Physiology</i> DESPOPOULOS Thieme, 2003, 448 pages, ISBN 1588900614</p> <p>A compact text with more than 150 colorful but complicated diagrams on the right and dense explanatory text on the left. Suffers from some translation problems. Overall, a unique, highly visual approach that is worthy of consideration. Useful as an adjunct to other review books.</p>	\$35.00	Review
B	<p><i>Clinical Physiology Made Ridiculously Simple</i> GOLDBERG MedMaster, 2001, 160 pages, ISBN 0940780216</p> <p>Easy reading with many amusing associations. The style does not work for everyone. Not as well illustrated as the rest of the series. Use as a supplement to other review books.</p>	\$19.95	Review

B***Lange Smart Charts: Physiology*****\$34.95**

Review

LYN

McGraw-Hill, 2004, 529 pages, ISBN 0071395075

Major topics in physiology organized into chart form according to body system. Includes mnemonics and definitions of key terms, but lacks detail at times. Suitable as an adjunct to another source. Limited student feedback.

B***Hematology at a Glance*****\$29.95**

Review

MEHTA

Blackwell Science, 2000, 128 pages, ISBN 0632047933

Covers common hematologic issues. Includes color illustrations. Presented in a logical sequence that is easy to read. Good for class use as well.

B***Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple*****\$18.95**

Review

PRESTON

MedMaster, 2002, 156 pages, ISBN 0960780313

Covers major electrolyte disturbances and fluid management issues with which medical students should be familiar. A great reference for the internal medicine clerkship. Provides information beyond the scope of the USMLE exam, but remains a useful companion for understanding physiology, kidney function, and fluids. Includes scattered diagrams and questions at the end of each chapter that test comprehension more than facts. Some questions involve calculations.

B***PreTest Physiology*****\$24.95**

Test/500 q

RYAN

McGraw-Hill, 2005, 480 pages, ISBN 0071436537

Questions with detailed, well-written explanations. The newest edition offers more USMLE-oriented questions as well as more focused explanations. One of the best of the *PreTest* series. May be useful for the motivated student following extensive review of other sources. Includes 32 pages of high-yield facts.

B-***Review Questions for Physiology*****\$24.95**

Test/700 q

PASLEY

CRC Press-Parthenon, 1998, 142 pages, ISBN 1850706018

Few clinical vignette-type questions. Answers are on the same page as the questions, making it easy to move through questions and check answers at the same time.

SECTION IV

Commercial Review Courses

- ▶ Kaplan Medical
- ▶ Northwestern Medical Review
- ▶ Postgraduate Medical Review Education (PMRE)
- ▶ The Princeton Review
- ▶ Youel's Prep, Inc.

Commercial preparation courses can be helpful for some students, but such courses are expensive and require significant time commitment. They are usually an effective tool for students who feel overwhelmed by the volume of material they must review in preparation for the boards. Note, too, that the multiweek review courses may be quite intense and may thus leave limited time for independent study. Also note that while some commercial courses are designed for first-time test takers, others focus on students who are repeating the examination. Still other courses focus on IMGs who want to take all three Steps in a limited amount of time. Finally, student experience and satisfaction with review courses are highly variable, and course content and structure can evolve rapidly. We thus suggest that you discuss options with recent graduates of review courses you are considering. Some student opinions can be found in discussion groups on the World Wide Web.

Kaplan Medical

Kaplan Medical offers a wide range of options for USMLE preparation, including live lectures, center-based study, and online products. All of its courses and products focus on providing the most exam-relevant information available.

Live Lectures. Kaplan's IntensePrep™ offers a highly structured, interactive live review led by expert faculty. Designed for medical students with little time to prepare, it includes approximately 15 days of live lectures during which faculty members cover the material students need to know to master the Step 1 exam. IntensePrep students also receive six months of access to Kaplan's online lectures, which offers more than 80 hours of high-yield, audio-streamed lectures. This course features seven volumes of lecture notes and a question book that includes 850 practice questions.

Kaplan also offers live-lecture courses ranging from 6 to 14 weeks with all-inclusive options to stay and study in high-end hotel accommodations, all of which are aimed at students who are repeating the exam as well as students and physicians who seek more time to prepare.

Center Study. CenterPrep 30 Visits, Kaplan's center-based lecture course, is designed for medical students seeking flexibility. It is offered at more than 120 Kaplan Centers across the United States and includes 30 visits to one Kaplan Center, where students are given access to approximately 175 hours of video lecture review. This course also includes seven volumes of lecture notes; a question book that includes 850 practice questions; and a full-length simulated exam with a complete performance analysis and detailed explanations. For those who would like more access to study resources, Kaplan offers CenterPrep, which includes a personalized study plan and three months of access to all Kaplan Centers.

Online Resources. Kaplan Medical provides online content and question-based review. WebPrep offers 80 hours of audio-streamed lectures, seven volumes of lecture notes, a full online Step 1 simulated exam, and access to its popular online question bank, Qbank, which contains over 2100 USMLE-style practice questions with detailed explanations. WebPrep is designed to be the most flexible content and question-based review available.

Kaplan Medical's online question review products have been updated to include the new USMLE-style functionality (the ability to highlight, annotate, and cross out). These resources are updated and revised each month to include new questions.

Kaplan's popular Qbank allows students to customize practice tests by discipline and organ system, receive instant on-screen feedback, and track their cumulative performance. Another Step 1 resource is Kaplan's Integrated Vignettes Qbank, an online clinical case question bank that allows users to practice

answering case-based, USMLE-style vignettes that are organized by symptom. Each vignette contains multidisciplinary questions covering different ways the underlying basic science concepts could be tested.

Kaplan's most comprehensive question practice option is Qreview, which contains more than 3500 questions and provides six months of simultaneous access to both Step 1 Qbank and IV Qbank. Qreview provides students with collective reporting of their results across both Qbanks and also includes an online simulated exam for further USMLE practice. Qbank demos are available at www.kaplanmedical.com.

More information on all of Kaplan's review options can be obtained at (800) 533-8850 or by visiting www.kaplanmedical.com.

Northwestern Medical Review

Northwestern Medical Review offers live-lecture review courses for both the COMLEX Level I and USMLE Step 1 examinations. Three courses (Plans) are available for each exam: NBI 100, a three-day course; NBI 200, a five-day course; and NBI 300, a 10- or 15-day course. All courses are in live-lecture format, and most are taught by the authors of the Northwestern Review Books. In addition to organized lecture notes and books for each subject, courses include Web-based CBT test-bank access and a large pool of practice questions and simulated exams. All plans are available in a customized, onsite format for groups of second-year students from individual U.S. medical schools. Additionally, public sites are frequently offered in East Lansing and Ann Arbor, Michigan; Philadelphia, Pennsylvania; St. Louis, Missouri; San Antonio, Texas; Los Angeles, California; and Long Island, New York. International sites may also be offered at the request of groups of students and international educational organizations.

Tuition for the USMLE Step 1 NBI 100 is \$310; NBI 200 is \$440; and NBI 300 ranges from \$890 to \$1030. Tuition is based on group size, program duration, and early-enrollment discounts. Home-study materials, CBT question-bank access, and DVD materials are also available for purchase independent of the live-lecture plans. Northwestern offers a retake option as well as a liberal cancellation policy.

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Postgraduate Medical Review Education (PMRE)

Established in 1976, PMRE offers complete home-study courses for the USMLE Step 1 in the form of audio cassettes and books. Home Study Package A offers 67 hours of live classes on audiotapes and a transcript book and a compilation of handout notes from the professors that you will hear on the cassettes for \$998. Package E features 9000 questions and answers on 20 hours of audiotape for \$250. PMRE uses professors who write questions for USMLE exams in conjunction with professionally recorded materials. PMRE is recognized by the AMA and The Federation Licensing Medical Examiners, Ft. Worth, Texas. Books are being sold at the UCLA medical book store, Barnes and Noble, and McGill Medical University book store, Montreal, Canada.

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The Princeton Review

The Princeton Review offers three flexible preparation options for the USMLE Step 1: the USMLE Online Course, the USMLE Classroom Course, and the USMLE Online Workout. In selected cities, The Princeton Review also offers a more intensive preparation course for IMGs.

USMLE Online Course. The USMLE Online Course offers comprehensive, self-paced preparation that includes the following:

- Seventy-five hours of online review, including lessons, vignettes, and drills
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- Twenty-four-hour e-mail support from Princeton Review Online instructors
- Three months of online access

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- Two thousand USMLE-style questions presented in the CBT format
- Three full-length diagnostic exams
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- More than 40 subject-specific drills
- A high-yield slide review for Anatomy and Pathology
- Complete explanations of all questions and answers
- Three months of access

More information can be found on The Princeton Review's Web site at www.princetonreview.com.

Youel's Prep, Inc.

Youel's Prep, Inc., has specialized in medical board preparation for 27 years. The company provides DVDs and videotapes (PowerPrep™, Quick Start™: the CD, Comprehensive Prep™ and Comprehensive Plus™), books (FastTrac Prep™ and 7 Steps to Board Success), live lectures (Youel's LivePrep™), and tutorials for small groups as well as for individuals (TutorialPrep™). All DVDs, videotapes, audiotapes, live lectures, and tutorials are correlated with a three-book set of Prep Notes© consisting of two textbooks, *Youel's Jewels I*© and *Youel's Jewels II*© (984 pages); and *Case Studies*, a question-and-answer book (1854 questions, answers, and explanations).

All Youel's Prep courses are taught and written by physicians, reflecting the clinical slant of the boards. All programs are systems based. In addition, all programs are updated continuously. Accordingly, books are not printed until the order is received.

Delivery in the United States is usually within one week. Optional express delivery is also available. Youel's Prep Home Study Program™—consisting of Youel's WebPrep, VideoPrep, AudioPrep, and BookPrep—allows students to own their materials and to use them for repetitive study in the convenience of their homes. Purchasers of any of the Youel's Prep programs are enrolled as members of the Youel's Prep Family of Students™, which affords them access to free telephone tutoring by Dr. Youel. Youel's Prep live lectures are held at select medical schools at the invitation of the school and students.

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APPENDIX

Abbreviations and Symbols

Abbreviation	Meaning	Abbreviation	Meaning
1°	primary	ARDS	adult respiratory distress syndrome
2°	secondary	Arg	arginine
3°	tertiary	ASA	acetylsalicylic acid
AA	amino acid	ASD	atrial septal defect
AAV	adeno-associated virus	ASO	antistreptolysin O
Ab	antibody	Asp	aspartic acid
ABP	androgen-binding protein	AST	aspartate transaminase
Ac-CoA	acetylcoenzyme A	AT	angiotensin
ACD	anemia of chronic disease	ATP	adenosine triphosphate
ACE	angiotensin-converting enzyme	ATPase	adenosine triphosphatase
ACh	acetylcholine	AV	atrioventricular
AChE	acetylcholinesterase	AVM	arteriovenous malformation
ACL	anterior cruciate ligament	AZT	azidothymidine
ACTH	adrenocorticotrophic hormone	BAL	British anti-Lewisite [dimercaprol]
ADA	adenosine deaminase, Americans with Disabilities Act	BMI	body-mass index
ADH	antidiuretic hormone	BMR	basal metabolic rate
ADHD	attention-deficit hyperactivity disorder	BP	blood pressure
ADP	adenosine diphosphate	BPG	bis-phosphoglycerate
AFP	α-fetoprotein	BPH	benign prostatic hyperplasia
Ag	antigen	BUN	blood urea nitrogen
AICA	anterior inferior cerebellar artery	CAD	coronary artery disease
AIDS	acquired immunodeficiency syndrome	cAMP	cyclic adenosine monophosphate
ALA	aminolevulinic acid	C-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
ALL	acute lymphocytic leukemia	CBSSA	Comprehensive Basic Science Self-Assessment
ALS	amyotrophic lateral sclerosis	CBT	computer-based testing
ALT	alanine transaminase	CCK	cholecystokinin
AML	acute myelocytic leukemia	CCl ₄	carbon tetrachloride
AMP	adenosine monophosphate	CCS	computer-based case simulation
ANA	antinuclear antibody	CCT	cortical collecting tubule
ANCA	antineutrophil cytoplasmic antibody	CD	cluster of differentiation
ANOVA	analysis of variance	CDP	cytidine diphosphate
ANP	atrial natriuretic peptide	CE	cholesterol ester
ANS	autonomic nervous system	CEA	carcinoembryonic antigen
AOA	American Osteopathic Association	CETP	cholesterol-ester transfer protein
AP	action potential	CF	cystic fibrosis
APC	antigen-presenting cell	CFU	colony-forming unit
APRT	adenine phosphoribosyltransferase	CFX	circumflex [artery]
APSAC	anistreplase	cGMP	cyclic guanosine monophosphate
AR	autosomal recessive	ChAT	choline acetyltransferase
ARC	Appalachian Regional Commission	CHF	congestive heart failure

Abbreviation	Meaning	Abbreviation	Meaning
CIN	candidate identification number, cervical intraepithelial neoplasia	DO	doctor of osteopathy
CJD	Creutzfeldt-Jakob disease	DOPA	dihydroxyphenylalanine (methyl dopa)
CK-MB	creatine kinase, MB fraction	2,3-DPG	2,3-diphosphoglycerate
CL	clearance	DPM	doctor of podiatric medicine
CLL	chronic lymphocytic leukemia	DPPC	dipalmitoyl phosphatidylcholine
CM	chylomicron	DS	double stranded
CML	chronic myeloid leukemia	dsDNA	double-stranded deoxyribonucleic acid
CMT	Computerized Mastery Test	dsRNA	double-stranded ribonucleic acid
CMV	cytomegalovirus	dTMP	thymidine-5'-phosphate
CN	cranial nerve	DTR	deep tendon reflex
CNS	central nervous system	DTs	delirium tremens
CO	cardiac output	dUMP	deoxyuridine monophosphate
CoA	coenzyme A	DVT	deep venous thrombosis
COGME	Council on Graduate Medical Education	EBV	Epstein-Barr virus
COMLEX	Comprehensive Osteopathic Medical Licensing Examination	EC ₅₀	median effective concentration
COMT	catechol-O-methyltransferase	ECF	extracellular fluid
COPD	chronic obstructive pulmonary disease	ECFMG	Educational Commission for Foreign Medical Graduates
COX	cyclooxygenase	ECG	electrocardiogram
C _p	plasma concentration	ECT	electroconvulsive therapy
CPAP	continuous positive airway pressure	ECV	effective circulating volume
CPK	creatine phosphokinase	ED ₅₀	median effective dose
CRH	corticotropin-releasing hormone	EDTA	ethylenediamine tetra-acetic acid
CSA	Clinical Skills Assessment	EDV	end-diastolic volume
CSF	cerebrospinal fluid, colony-stimulating factor	EEG	electroencephalogram
CT	computed tomography	EF	ejection fraction, elongation factor
CVA	cardiovascular accident, costovertebral angle	ELISA	enzyme-linked immunosorbent assay
Cx	complication	EM	electron micrograph, electron microscopic, electron microscopy
Cys	cysteine	EMB	eosin-methylene blue
d4T	didehydrodeoxythymidine [stavudine]	EOM	extraocular muscle
DAF	decay-accelerating factor	epi	epinephrine
DAG	diacylglycerol	EPO	erythropoietin
dATP	deoxyadenosine triphosphate	EPS	extrapyramidal system
ddC	dideoxycytidine	ER	endoplasmic reticulum
ddI	didanosine	ERAS	Electronic Residency Application Service
DES	diethylstilbestrol	ERCP	endoscopic retrograde cholangiopancreatography
DHAP	dihydroxyacetone phosphate	ERP	effective refractory period
DHB	dihydrobiopterin	ERPF	effective renal plasma flow
DHEA	dehydroepiandrosterone	ERV	expiratory reserve volume
DHF	dihydrofolic acid	ESR	erythrocyte sedimentation rate
DHPG	dihydroxy-2-propoxymethyl guanine	ESV	end-systolic volume
DHS	Department of Homeland Security	EtOH	ethyl alcohol
DHT	dihydrotestosterone	FAD	oxidized flavin adenine dinucleotide
DI	diabetes insipidus	FADH ₂	reduced flavin adenine dinucleotide
DIC	disseminated intravascular coagulation	FAP	familial adenomatous polyposis
DIP	distal interphalangeal [joint]	5f-dUMP	5-fluorodeoxyuridine monophosphate
DIT	diiodotyrosine	FE _{Na}	excreted fraction of filtered sodium
DKA	diabetic ketoacidosis	FEV ₁	forced expiratory volume in 1 second
DNA	deoxyribonucleic acid	FF	filtration fraction
2,4-DNP	2,4-dinitrophenol	FFA	free fatty acid
		FGF	fibroblast growth factor

Abbreviation	Meaning	Abbreviation	Meaning
FLEX	Federation Licensing Examination	HHS	[Department of] Health and Human Services
f-met	formylmethionine	HHV	human herpesvirus
FMG	foreign medical graduate	5-HIAA	5-hydroxyindoleacetic acid
FMN	flavin mononucleotide	His	histidine
FRC	functional residual capacity	HIV	human immunodeficiency virus
FSH	follicle-stimulating hormone	HLA	human leukocyte antigen
FSMB	Federation of State Medical Boards	HMG-CoA	hydroxymethylglutaryl-coenzyme A
FTA-ABS	fluorescent treponemal antibody—absorbed	HMP	hexose monophosphate
5-FU	5-fluorouracil	HMWK	high-molecular-weight kininogen
FVC	forced vital capacity	HNPPC	hereditary nonpolyposis colorectal cancer
G3P	glucose-3-phosphate	hnRNA	heterogeneous nuclear ribonucleic acid
G6P	glucose-6-phosphate	HPA	hypothalamic-pituitary-adrenal [axis]
G6PD	glucose-6-phosphate dehydrogenase	HPSA	Health Professional Shortage Area
GABA	γ -aminobutyric acid	HPV	human papillomavirus
GBM	glomerular basement membrane	HR	heart rate
G-CSF	granulocyte colony-stimulating factor	HSV	herpes simplex virus
GFAP	glial fibrillary acid protein	HSV-1	herpes simplex virus 1
GFR	glomerular filtration rate	HSV-2	herpes simplex virus 2
GGT	γ -glutamyl transpeptidase	5-HT	5-hydroxytryptamine (serotonin)
GH	growth hormone	HTLV	human T-cell leukemia virus
GI	gastrointestinal	HUS	hemolytic-uremic syndrome
GIP	gastric inhibitory peptide	IBD	inflammatory bowel disease
GIST	gastrointestinal stromal tumor	IC	inspiratory capacity
Glu	glutamic acid	ICA	internal carotid artery
GM-CSF	granulocyte-macrophage colony-stimulating factor	ICF	intracellular fluid
GMP	guanosine monophosphate	ICP	intracranial pressure
GN	glomerulonephritis	ID ₅₀	median infectious dose
GnRH	gonadotropin-releasing hormone	IDDM	insulin-dependent diabetes mellitus
GPe	globus pallidus externa	IDL	intermediate-density lipoprotein
GPi	globus pallidus interna	I/E	inspiratory/expiratory [ratio]
GRP	gastrin-releasing peptide	IF	immunofluorescence
GSH	reduced glutathione	IFN	interferon
GSSG	oxidized glutathione	Ig	immunoglobulin
GTP	guanosine triphosphate	IHSS	idiopathic hypertrophic subaortic stenosis
GU	genitourinary	IL	interleukin
HAART	highly active antiretroviral therapy	Ile	isoleucine
HAV	hepatitis A virus	IMA	inferior mesenteric artery
Hb	hemoglobin	IMED	International Medical Education Directory
HBcAb	hepatitis B core antibody	IMG	international medical graduate
HBcAg	hepatitis B core antigen	IMP	inosine monophosphate
HBeAb	hepatitis B early antibody	IND	Investigational New Drug
HBeAg	hepatitis B early antigen	INH	isonicotine hydrazine [isoniazid]
HBsAb	hepatitis B surface antibody	IP ₃	inositol triphosphate
HBsAg	hepatitis B surface antigen	IPV	inactivated polio vaccine
HBV	hepatitis B virus	IRV	inspiratory reserve volume
hCG	human chorionic gonadotropin	ITP	idiopathic thrombocytopenic purpura
HCV	hepatitis C virus	IV	intravenous
HDL	high-density lipoprotein	IVC	inferior vena cava
HDV	hepatitis D virus	JG	juxtaglomerular [cells]
HEV	hepatitis E virus	JGA	juxtaglomerular apparatus
HGPRTase	hypoxanthine-guanine phosphoribosyltransferase		

Abbreviation	Meaning	Abbreviation	Meaning
KSHV	Kaposi's sarcoma-associated herpesvirus	MTP	metatarsophalangeal [joint]
LA	left atrial	MUA/P	Medically Underserved Area and Population
LAD	left anterior descending [artery]	MVO ₂	myocardial oxygen consumption
LCA	left coronary artery	NAD ⁺	oxidized nicotinamide adenine dinucleotide
LCAT	lecithin-cholesterol acyltransferase	NADH	reduced nicotinamide adenine dinucleotide
LCL	lateral collateral ligament	NADP ⁺	oxidized nicotinamide adenine dinucleotide phosphate
LCME	Liaison Committee on Medical Education	NADPH	reduced nicotinamide adenine dinucleotide phosphate
LCV	lymphocytic choriomeningitis virus	NBME	National Board of Medical Examiners
LDH	lactate dehydrogenase	NBOME	National Board of Osteopathic Medical Examiners
LDL	low-density lipoprotein	NBPME	National Board of Podiatric Medical Examiners
LES	lower esophageal sphincter	NDA	New Drug Application
Leu	leucine	NE	norepinephrine
LFA-1	leukocyte function-associated antigen 1	NF	neurofibromatosis
LFT	liver function test	NH ₃	ammonia
LGN	lateral geniculate nucleus	NIDDM	non-insulin-dependent diabetes mellitus
LH	luteinizing hormone	NK	natural killer [cells]
LLQ	left lower quadrant	NPV	negative predictive value
LM	light microscopy	NSAID	nonsteroidal anti-inflammatory drug
LMN	lower motor neuron	OAA	oxaloacetic acid
LSE	Libman-Sacks endocarditis	OCD	obsessive-compulsive disorder
LT	leukotriene	OCP	oral contraceptive pill
LV	left ventricle, left ventricular	OMT	osteopathic manipulative technique
Lys	lysine	OPV	oral polio vaccine
MAC	membrane attack complex	OR	odds ratio
MAO	monoamine oxidase	PA	posteroanterior
MAOI	monoamine oxidase inhibitor	PABA	para-aminobenzoic acid
MAP	mean arterial pressure	PAH	para-aminohippuric acid
MCA	middle cerebral artery	PALS	periarterial lymphatic sheath
MCHC	mean corpuscular hemoglobin concentration	PAN	polyarteritis nodosa
MCL	medial collateral ligament	P-ANCA	perinuclear antineutrophil cytoplasmic antibody
MCP	metacarpophalangeal [joint]	PAS	periodic acid Schiff
MCV	mean corpuscular volume	PC	pyruvate carboxylase
MEN	multiple endocrine neoplasia	PCL	posterior cruciate ligament
MEOS	microsomal ethanol oxidizing system	PCP	phencyclidine hydrochloride, <i>Pneumocystis carinii</i> pneumonia
Met	methionine	PCR	polymerase chain reaction
MGN	medial geniculate nucleus	PCWP	pulmonary capillary wedge pressure
MHC	major histocompatibility complex	PD	posterior descending [artery]
MHPSA	Mental Health Professional Shortage Area	PDA	patent ductus arteriosus
MI	myocardial infarction	PDE	phosphodiesterase
MIT	monoiodotyrosine	PDH	pyruvate dehydrogenase
MLF	medial longitudinal fasciculus	PE	pulmonary embolism
MMR	measles, mumps, rubella [vaccine]	PEP	phosphoenolpyruvate
6-MP	6-mercaptopurine	PFK	phosphofructokinase
MPO	myeloperoxidase	PFT	pulmonary function test
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	PG	prostaglandin
MRI	magnetic resonance imaging		
mRNA	messenger ribonucleic acid		
MRSA	methicillin-resistant <i>S. aureus</i>		
MS	multiple sclerosis		
MSH	melanocyte-stimulating hormone		

Abbreviation	Meaning	Abbreviation	Meaning
Phe	phenylalanine	SER	smooth endoplasmic reticulum
PICA	posterior inferior cerebellar artery	SEVIS	Student and Exchange Visitor Information System
PID	pelvic inflammatory disease	SEVP	Student and Exchange Visitor Program
PIP	proximal interphalangeal [joint]	SGOT	serum glutamic oxaloacetic transaminase
PIP ₂	phosphatidylinositol 4,5-bisphosphate	SGPT	serum glutamic pyruvate transaminase
PK	pyruvate kinase	SHBG	sex hormone-binding globulin
PKD	polycystic kidney disease	SIADH	syndrome of inappropriate antidiuretic hormone
PKU	phenylketonuria	SLE	systemic lupus erythematosus
PML	progressive multifocal leukoencephalopathy	SLL	small lymphocytic lymphoma
PMN	polymorphonuclear [leukocyte]	SMA	superior mesenteric artery
PNET	primitive neuroectodermal tumor	SMX	sulfamethoxazole
PNH	paroxysmal nocturnal hemoglobinuria	SNc	substantia nigra compacta
PNS	peripheral nervous system	snRMP	small nuclear ribonucleoprotein
POMC	pro-opiomelanocortin	SOD	superoxide dismutase
PPRF	paramedian pontine reticular formation	SR	sarcoplasmic reticulum
PPV	positive predictive value	SRP	sponsoring residency program
PRPP	phosphoribosylpyrophosphate	SRS-A	slow-reacting substance of anaphylaxis
PSA	prostate-specific antigen	SS	single stranded
PSS	progressive systemic sclerosis	ssDNA	single-stranded deoxyribonucleic acid
PT	prothrombin time	SSPE	subacute sclerosing panencephalitis
PTH	parathyroid hormone	SSRI	selective serotonin reuptake inhibitor
PTHrP	parathyroid hormone-related protein	ssRNA	single-stranded ribonucleic acid
PTSD	post-traumatic stress disorder	STD	sexually transmitted disease
PTT	partial thromboplastin time	STN	subthalamic nucleus
PV	plasma volume	SV	sinus venosus, stroke volume
RA	rheumatoid arthritis	SVC	superior vena cava
RBC	red blood cell	SVT	supraventricular tachycardia
RBF	renal blood flow	t _{1/2}	half-life
RCA	right coronary artery	T ₃	triiodothyronine
RDS	respiratory distress syndrome	T ₄	thyroxine
RDW	red-cell distribution width	TB	tuberculosis
REM	rapid eye movement	TBG	thyroxine-binding globulin
RER	rough endoplasmic reticulum	TBW	total body water
RNA	ribonucleic acid	3TC	dideoxythiacytidine [lamivudine]
RPF	renal plasma flow	TCA	tricarboxylic acid [cycle], tricyclic antidepressant
RPR	rapid plasma reagin	Tc cell	cytotoxic T cell
RR	relative risk, respiratory rate	TCR	T-cell receptor
rRNA	ribosomal ribonucleic acid	TD ₅₀	median toxic dose
RS	Reed-Sternberg [cells]	TFT	thyroid function test
RSV	respiratory syncytial virus	TG	triglyceride
RUQ	right upper quadrant	TGF	transforming growth factor
RV	right ventricle, right ventricular, residual volume	THB	tetrahydrobiopterin
RVH	right ventricular hypertrophy	Th cell	helper T cell
SA	sinoatrial, subarachnoid	THF	tetrahydrofolate
SAM	S-adenosylmethionine	Thr	threonine
SARS	severe acute respiratory syndrome	TIBC	total iron-binding capacity
SC	subcutaneous	TLC	total lung capacity
SCID	severe combined immunodeficiency disease	TMP-SMX	trimethoprim-sulfamethoxazole
SD	standard deviation, subdural		
SEM	standard error of the mean		
SERM	selective estrogen receptor modulator		

Abbreviation	Meaning	Abbreviation	Meaning
TN	trigeminal neuralgia	USIA	United States Information Agency
TNF	tumor necrosis factor	USMLE	United States Medical Licensing Examination
TNM	tumor, node, metastases [staging]	UTI	urinary tract infection
TOEFL	Test of English as a Foreign Language	UV	ultraviolet
tPA	tissue plasminogen activator	VA	ventral anterior, Veterans Administration
TPP	thiamine pyrophosphate	Val	valine
TPR	total peripheral resistance	VC	vital capacity
TRAP	tartrate-resistant acid phosphatase	V _d	volume of distribution
TRH	thyrotropin-releasing hormone	VDRL	Venereal Disease Research Laboratory
tRNA	transfer ribonucleic acid	VEGF	vascular endothelial growth factor
Trp	tryptophan	VF	ventricular fibrillation
TSH	thyroid-stimulating hormone	VIP	vasoactive intestinal peptide
TSI	thyroid-stimulating immunoglobulin	VIPoma	vasoactive intestinal polypeptide-secreting tumor
TSS	toxic shock syndrome	VLDL	very low density lipoprotein
TSST	toxic shock syndrome toxin	VMA	vanillylmandelic acid
TTP	thrombotic thrombocytopenic purpura	VPL	ventral posterior nucleus, lateral
TV	tidal volume	VPM	ventral posterior nucleus, medial
TXA	thromboxane	VPN	ventral posterior nucleus
UA	urinalysis	V/Q	ventilation/perfusion [ratio]
UCV	Underground Clinical Vignettes	VSD	ventricular septal defect
UDP	uridine diphosphate	VZV	varicella-zoster virus
UMN	upper motor neuron	WBC	white blood cell
URI	upper respiratory infection	XR	X-linked recessive
USDA	United States Department of Agriculture		